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INSTITUTE FOR THE STUDY OF
ANALGESIC AND SEDATIVE DRUGS

II

THE SALICYLATES

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A Critical Bibliographic Review

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Note on Reference Citations and on Use of the Bibliography

ORGANIZATION. The Bibliography is arranged alphabetically and the references are numbered in alphabetic order. Unsigned articles or books have been placed together at the end of the Bibliography and are listed there (beginning with No. 3838) in the alphabetic order of journals or publishers.

Works dealing with or directly pertinent to salicylates have been included in the Bibliography. Collateral references are cited in footnotes to the text.

ABBREVIATIONS. The names of periodicals have been abbreviated in accordance with the style of *A World List of Scientific Periodicals* (2d ed. London; Oxford Univ. Press, 1934).

CITATION BY YEAR OF PUBLICATION. The names of authors mentioned in the text are usually followed by the year of publication of the cited work. The year of publication is always shown in the text in *italics* within square brackets; e.g., Smith [1932]. The reference can be found in the Bibliography in alphabetic order under the author's name.

CITATION BY REFERENCE NUMBER. In the case of unsigned articles, or when it has been more convenient to omit the names of authors in the text, the work is cited by the Reference Number. Reference Numbers in the text are always shown in regular type within parentheses; e.g., Several investigators (18, 524, 1932, 3076). These references can be located in the Bibliography by their numbers.

In some instances, where the author's name and the year of publication may be insufficient to identify the reference, both the year and the Reference Number are given; e.g., Smith and his associates [1946 (3274)]. When an author has more than one publication of the same year listed in the Bibliography but only one is cited in the text, the intended reference can be identified by the listing, at the end of each bibliographic entry, of the pages in the text where the work is cited.

LISTS OF ADDITIONAL REFERENCES. In the lists of Additional References which appear under various subject headings at the

end of most chapters, and at the end of sections in Chapter V, the citations are by Reference Number only.

ASTERISKS. An asterisk at the end of a reference in the Bibliography denotes that an abstract of the work is available in the files of the Critical Reviews in Medicine and Biology at the Laboratory of Applied Physiology, Yale University.

REFERENCE TO ABSTRACTS. To facilitate consultation of sources by users of the Bibliography to whom the original works may not be available, references to published abstracts of the works cited, when known, have been listed following each title.

LANGUAGE OF REFERENCES. Titles in French, German, Italian and Spanish are given in the original language. Titles from other languages have been translated into English. Titles cited in other than the original language are enclosed in square brackets.

Author Index. The numbers in *italics* which appear following many of the bibliographic entries, separated from the reference by a left-hand square bracket, denote the pages of the text where the work is cited. By referring to these numbers the Bibliography may be used as an index of authors cited.

Abbreviations

g.	gram(s)
gr.	grain(s)
kg.	kilogram(s)
mg.	milligram(s)
mg. per kg.	milligram(s) per kilogram of body weight

Introduction

THIS volume, dealing with the salicylates, is the second in a series of critical reviews of the literature on analgesic and sedative drugs. The first to be published dealt with acetanilid; others now in preparation deal with antipyrine, phenacetin and bromides.

The study here, in contrast to the one on acetanilid, deals not with a single drug but with a radical capable of many combinations. Of the great number of salicylate compounds, only those were included in the review which are or have been given with therapeutic intent; and from among these were omitted those in which the salicylate radical is used only to form a salt of another more potent drug, as caffeine sodium salicylate or physostigmine salicylate.

Again in contrast to the analgesic drugs that form the subjects of other volumes in this series, salicylates are widely used as a specific medicament. Much important material, particularly on toxicity, is to be found in the literature on rheumatic disease, which was therefore dealt with at some length. In contrast, the reader will find certain sections dealing with analgesic action in various diseases shortened to little more than bibliographical references. When the analgesic action of salicylate was first coming into prominence, the effects of salicylates were tried and reported upon for almost every painful disease. The uniform findings indicate only a general analgesic action and justify no separate descriptions.

It is hoped that for the investigator in this field the review will serve a useful purpose not only in bringing to hand the literature but in pointing out desirable lines of investigation and guiding away from duplication of study.

The bibliography upon which this volume is based contains more than 4,000 references. An effort was made to review the entire pertinent literature but because of conditions during and after the war it was impossible to obtain certain issues of some journals in foreign languages. In these circumstances it was necessary to rely upon abstracts. These instances, which are few in number, are indicated in the bibliography.

HOWARD W. HAGGARD, M.D.

Historical

THE naturally occurring salicylates* found in the bark, leaves and fruit of many plants and trees are ancient remedies. Thus Hippocrates some 2,400 years ago recommended juice of the poplar tree for eye diseases, and leaves of the willow tree in childbirth. Celsus during the first century A.D. employed willow leaves boiled in vinegar for prolapse of the uterus. Pliny, although not a practicing physician, in the first century encyclopedized the popular and medical knowledge of his time and he mentioned uses for salicylate which were more in line with modern therapy than those in the recommendations of Hippocrates and Celsus: a paste made from the ash of willow bark for removing corns and callosities; an infusion of the poplar bark for sciatica; and the leaves of the same tree sodden in vinegar as a cataplasm for gout. In addition, he recommended the juice of the willow tree as a diuretic and the gum of the poplar for cleansing the eyes.

Dioscorides, of the same period, used a decoction of willow leaves or of the ash of willow bark for the removal of corns and in treating earache, skin diseases and gout. Galen in the second century used willow leaves for bloody wounds and for ulcers, fistulas and erysipelas. Quintus Serenus Samonicus (3186) in a commentary on Celsus recommended the use of willow leaves and bark in the treatment of podagra. In the writings from the School of Salerno in the eleventh century, willow is offered as a vermifuge and as a remedy for diseases of the eyes and the liver (3023, 3520).

In the herbals that formed the basis of home and medical therapy of the Middle Ages (3486) and the Renaissance—and even later (3010a, 3486, 3898a, 4076a)—the salicylate-bearing barks, leaves and fruits were given the therapeutic uses mentioned by the earlier writers along with some additions such as that of Gerarde (see 3023), in the seventeenth century, who recommended the leaves and bark of willow in the prevention and treatment of “spitting of blood and all other fluxes of blood whatsoever in man or woman.” Boerhave in 1751 reaffirmed the usefulness of salicylate as a diuretic and employed “*Lachrima betulae*” of the birch tree.

*They exist mainly as salicin and methyl salicylate.

Capit. CCCLVII. Capit. CLVIII ~

Salix ein weide



Salix vel salamentum latine.
 grece fice. arabice kuleff.
 Der meister Scrapio in dem
 buch aggregatons in dē capitul hnt
 less. beschreidet vñ vñ spuchet die
 bleter vñ dy blümē vñ vñ seid fast
 truckel machē. vñ dyerindē vñ wyde
 fere vñ dyerindē vñ wyde

Scordeon mild
 knoblauch.



der scordeon.

FIGURE 1.—Medical use of various parts of the willow tree as described in an anonymous Swiss herbal, *Herbarius zu Deutsch: Gart der Gesundheit*. [Ca. 1486.]

Deutsches Apotheken I Theil. 103
 Von Winter Grün. Cap. LXI.

Stammen des Winter grüns vnd desselbigen erklerung.



Jewel wie edlicher

inn rechter ordnung die aller gebräuchlichsten
 vnd nützlichste Wundkreutter auff das fleys
 sigst zu beschreiben/ vnder welchen der Winter
 grünn die geringste/ welcher diesen namen der
 vrsach halb empfangen/ das er den frost vnd

goldt/ aber der gemeinst vnd gebräuchlichste
 nammt/ so er bey den Apothekern vnd Wunders
 ärzten dieser zeyt noch behalten hat/ ist Pyro
 la/ darumb das sich seine blätter dem Rierbaß
 laub vergleichen/ eilich nennen/ in auch Walde
 Kölen Holzmangolt/ welchen namen alle vn
 der die Lateinischen namen Beta Sylvestris
 begriffen sind/ wiewol auch andie kreutter
 darnit gemeint werden/ wie du folgentz weyß
 er bitten wirst.

Eygenliche beschreibung der form vnd ge
 stalt des Wintergrüns.

FIGURE 2.—Description and medical use of the wintergreen plant in the herbal of W. H. Ryff [1573].

Even up to this late date no mention had been made of one of the most striking actions of salicylate, that of antipyresis. This use of willow bark by the medical profession dates from a report made in 1763 by the Reverend Edward Stone (3360) to the President of the Royal Society. He stated that, from experiments, he had found that the bark of willow trees had an "extraordinary bitterness" and he therefore thought it might have the antipyretic qualities of the Peruvian bark. In addition there was some teleological thinking: "As this tree delights in a moist or wet soil, where agues chiefly abound, the general maxim, that many natural maladies carry their cures along with them, or that their remedies lie not far from their causes, was so very apposite to this particular case, that I could not help applying it; and that this might be the intention of Providence here, I must own had some little weight with me." He dried the bark, powdered it, and gave it in doses of about 20 gr. to a dram every 4 hours in some 50 cases of "agues and intermitting disorders," sometimes together with Peruvian bark. He claimed that he obtained good results.

Although it was the report of the Reverend Mr. Stone that called the physicians' attention to salicylate as an antipyretic, it appears that this action had long been observed, though not reported, in home medication. Thus Longmore in 1798, in describing the poisoning of 14 soldiers in Quebec who had drunk tea containing *Gaultheria*, stated that the substance "is frequently used by the Canadians, and is said to be a cooling and grateful ptisan in fevers." In 1838 Buchner (see 278) wrote in the *Lehrbuch der Chemie* that the use of willow bark as an antipyretic had long been known and Cazin in 1858 stated that French peasants had long employed decoctions of willow bark in treating fevers.

Following the report of Stone the use of the willow bark was frequently reported on and recommended as both an antipyretic and an analgesic but mainly as a substitute for the rare and expensive Peruvian bark. These recommendations appear in the writings of the anonymous author (3895) of *L'Albert Moderne* [1772], of Gunzius (see 3345) in 1772, of Samuel James [1792], of van Geuns (3559) in 1778, of Wilkinson [1803], and of Sobernheim [1847]. The *Lexicon-Medicum* of Robert Hooper, printed in New York in 1826, states that the bark of different species of willow trees "is recommended as a good substitute for Peruvian bark, and is said to cure intermittents and other diseases requiring tonic and

adstringent remedies." White reported in 1798 that "Since the introduction of this bark into practice at the Bath City Infirmary and Dispensary, as a substitute for the Cinchona, not less than twenty pounds a year have been saved to the Charity." White tried to explore the chemical nature of the active substance in the willow bark; he discovered the color reaction with iron salts which is still in use in the determination of salicylates.

During the nineteenth century there was keen interest in the chemical structure and properties of the active substance in willow bark. In 1826 Brugnatelli and Fontana announced salicin as the active principle of the bark, and in 1829 Leroux isolated this glucoside in the pure state [both cit. Sharp (3201)]. Piria [1838] is generally credited with having first prepared salicylic acid from salicin. Tschirch [1917], however, states that the Swiss pharmacist Pagenstecher obtained salicylaldehyde by distilling the flowers of *Spirea ulmaria*. He transmitted this information to Löwig who, in 1835, obtained salicylic acid ("Spirsäure") by oxidation of the aldehyde.

The modern history of the salicylates starts in 1874 when synthetic salicylic acid became available through a procedure developed by Kolbe and Lautemann. Kolbe (1923) wrote in 1860 that phenyl-oxyhydrate in which sodium is dissolving forms salicylic acid with carbonic acid, hydrogen being freed. Kolbe and Lautemann (1930) are often erroneously cited as the first to produce salicylic acid synthetically. In reality Gerland found in 1852 that he could synthesize salicylic acid by the action of nitrous acid on anthranilic acid (o-aminobenzoic acid). In 1855 Bertagnini reported that after administration of salicylic acid it is eliminated in the urine and conjugated with glycocholic acid as salicyluric acid.

Salicylic acid was soon found to have antiseptic properties which would preserve milk and meat; it was even recommended to replace phenol, which at that time was the antiseptic in use in surgery. The antipyretic quality of the drug in infectious diseases was for a time attributed to its antiseptic action. When the sodium salt, however, which has only slight antiseptic qualities, was shown to have antipyretic qualities equal to those of the acid, that theory was abandoned.

In the late nineteenth century a great number of clinical reports record the use of salicylates in the treatment of a wide variety of diseases. The one important fact which evolved from these publi-

cations was the use of salicylates in rheumatic disease. Stricker started clinical work with salicylates in the latter part of 1875 and reported in 1876 that this medicament was not only an antipyretic but also a specific remedy for rheumatic fever. Two months later T. MacLagan (2262) published his observations on the use of salicylate in eight cases of rheumatic fever; his work had been started in 1874 and therefore anteceded that of Stricker although his publication appeared later. MacLagan reported that on the administration of salicylate, pains and fever disappeared and that, when given in acute cases "at the commencement of the attack, it seems sometimes to arrest the course of the malady."

Again as with the antipyretic action, the use of salicylate-containing drugs in rheumatic fever was new to physicians but not to the layman. Pribram [1901] relates that soon after the publication of his paper MacLagan received a letter from Dr. Ensor at Cape of Good Hope in which he stated that the Hottentots in Africa had for a long time used the bark of willow trees in treating rheumatic diseases. Perhaps the earliest reference to the use of salicylates in inflammatory rheumatism is found in *Dr. Chase's Recipes, or Information for Everybody*, printed in Ann Arbor, Michigan, in 1865. According to this author a concoction of the bark of yellow poplar, dogwood, prickly ash, wild cherry and white ash trees in water, given with rye whisky, was recommended by David Mowry of Greenville, Ohio, for the treatment of inflammatory rheumatism.

The natural salicylates are little employed today. They have been replaced largely by sodium salicylate, phenyl salicylate, methyl salicylate and acetylsalicylic acid. Salol was produced by von Nencki [1885] and introduced into medicine by Sahli in 1886. It was for a time widely used for the treatment of rheumatic fever, and also as a disinfectant of the intestinal and urinary tracts. Methyl salicylate, formerly obtained from the leaves of *Gaultheria procumbens* or the bark of *Betula lenta* is now produced by esterification of salicylic acid with methanol. It is widely used for external application in muscular rheumatism and similar ailments and as a flavoring in soft drinks and candies.

Acetylsalicylic acid was prepared by the chemist von Gerhardt [1853] from the action of acetylchloride on sodium salicylate, and later by von Gilm [1859]. For many years it was a rare substance of use in chemical laboratories but with no therapeutic application. Its therapeutic use was one of chance. The father of F. Hoffmann

(see 1524), suffering from rheumatic arthritis and unable to stand prolonged treatment with salicylic acid, induced his son, who was associated with the chemical works of Bayer in Elberfeld, Germany, to try some salicylate compounds which could be better tolerated. Acetylsalicylic acid was tried with success. In 1899 this drug was introduced into medical practice by Wohlgemut and by Dreser. It was first widely used to replace sodium salicylate especially in the treatment of rheumatic diseases. Soon, however, the strong analgesic action of this particular salicylate compound was recognized and its greatest use became that of relief of pain, particularly muscular pain and headache. Today it is perhaps the most widely used of all medicaments. In the United States alone the average production in the period 1935 to 1944 was more than 6 million pounds per year.

The intravenous injection of salicylates offers the most recent variation to the medication by these substances; Dr. P. A. Blanchier had found, as early as 1879, that sodium salicylate in neutral solution was safe for injection directly into the blood of mammals, but Mariani in 1902 was the first to use it in patients [see Seguron (3155)]. Mendel (2383), who was the first to administer digitalis intravenously, used intravenous injections of sodium salicylate in 1904.

The intravenous application of salicylates for the treatment of rheumatic fever has been revived recently by Coburn [1943] and employed in conjunction with determinations of the concentration of salicylate in the blood.

Chapter II

Occurrence and Properties of Salicylates

NATURAL OCCURRENCE

BEFORE salicylates were prepared synthetically, they were extracted from a variety of plants. Of these, there are essentially two groups, one yielding salicin, the other methyl salicylate glycosides.

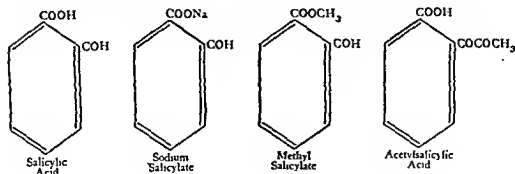
Salicin occurs in the poplar and willow trees and in the black haw (217, 1050, 1270, 1729, 1807, 2203, 3020, 3309).

Methyl salicylate glycosides occur in birch and beech trees as well as in *Gaultheria procumbens*, partridge berry, chequerberry, wintergreen, *Gaultheria hispidula*, wild pansy, milkwort, bay tree, Indian licorice, soap berry, olive, madder, jasmine, myrtle, linden, buckthorn, various grasses, coffee, and in the following botanical orders: Leguminosae, Euphorbiaceae, Bixineae, Cupuliferae and Erythrixyleae (92, 107, 299, 720, 1270, 1613, 2199, 2203, 2712, 2797, 2812, 2814, 3020, 3176, 3358, 3430, 3623, 3745, 3841, 3968, 3969).

Salicylates in small amounts have been reported in common fruits such as the orange, strawberry, apple, cherry, plum, raspberry and grape (868, 2712, 3973). In addition, they have been found in the woodruff, marigold, hyacinth, tulip, yucca, clover, yellow bird's-nest, meadowsweet, ipecacuanha, mignonette, ammoniac plant, Americaeae family, and pansy (299, 310, 483, 868, 1367, 2203, 2712, 3071, 3309, 3700, 3779, 3969).

Salicylates have been reported as occurring in one animal product, the beaver castor (2041).

FORMULAS AND SYNONYMS OF SALICYLATE COMPOUNDS



All salicylates are derivatives of o-hydroxybenzoic acid. Of the three isomers of hydroxybenzoic acid only the ortho compound (salicylic acid) has come into medical use. It is white in color, acid in taste, and irritating to the stomach when taken in large doses. It has been replaced for internal use by a number of salts or esters of which sodium salicylate, acetylsalicylic acid and methyl salicylate are the most important. Most of the salicylates used for therapeutic purposes are formed by substitution on the carboxyl group, but in the one most widely used, acetylsalicylic acid, substitution is on the hydroxyl group.

Table 1* gives the chemical names and the official and non-official pharmaceutical and trade names of the salicylate compounds most frequently mentioned in the medical literature. The content of salicylic acid is expressed in grams of salicylic acid equivalent to 1 g. of the compound.

TABLE 1.—*Salicylate Compounds*

No.	Chemical, Pharmaceutical and Trade Names	Formula	Grams Salicylic Acid Molecular Weight Equivalent to 1 g. of Drug	
1	Acetyl-p-amino-phenyl salicylate acetylparamidosalol acetylparaminosalolum phenetsal salophen	$\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{OC}_6\text{H}_4 \cdot \text{NHCOCH}_3$	271.11	0.51
2	Acetylsalicylic acid acetilum acidulatum acetophen acetol acetosal acetosalic acid acetosalin aceticyl acetylin acetylsal acidum acetylsalicylicum acylpyrin aspirin aspro	$\text{CH}_3 \cdot \text{CO} \cdot \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{COOH}$	180.06	0.77

*Table 1 was computed chiefly from Hodgman and Holmes, *Handbook of Chemistry and Physics*, 25th ed., Cleveland, Ohio, Chemical Rubber Co., 1941; *The Merck Index*, 5th ed., Rahway, N. J., Merck & Co., 1940; and Dohrn and Thiele [1911].

TABLE 1.—Cont.

No.	Chemical, Pharmaceutical and Trade Names	Formula	Grams Salicylic Acid Molecular Equivalent to 1 g. of Weight Drug	
	empirin			
	helicon			
	rhodine			
	salacetin			
	salcetogen			
	saletin			
	xaxa			
3	Aminopyrine salicylate pyramidon salicylate	$C_{13}H_{17}ON_3 \cdot C_7H_6O_3$	369.20	0.37
4	Ammonium salicylate ammonii salicylas	$HO \cdot C_6H_4 \cdot COONH_4$	155.08	0.89
5	Amyl salicylate ulmaren	$HO \cdot C_6H_4 \cdot CO_2 \cdot C_5H_{11}$	208.13	0.66
6	Antipyrine salicylate phenazone salicylate salazolon salipyrizolon salipyrine	$C_{11}H_{12}N_2O \cdot C_7H_6O_3$	326.16	0.42
7	Bornyl salicylate salit	$C_{10}H_{17}O \cdot CO \cdot C_6H_4 \cdot OH$	274.17	0.50
8	Calcium acetyl-salicylate kalmopyrin kalsetal soluble aspirin tylcalsin	$(CH_3CO \cdot O \cdot C_6H_4COO)_2Ca \cdot 2H_2O$	434.22	0.64
9	Calcium salicylate calcii salicylas	$(OH \cdot C_6H_4 \cdot COO)_2Ca \cdot 2H_2O$	350.19	0.79
10	Cinchonidine salicylate cinchonidinae salicylas	$C_{19}H_{22}N_2O \cdot C_7H_6O_3$	432.23	0.32
11	Ethylglycolic acid ester of salicylic acid	$\cdot COOH \cdot C_4H_8OOC \cdot CH_2OC_2H_5$	224.11	0.62

TABLE 1.—Cont.

No.	Chemical, Pharmaceutical and Trade Names	Formula	Grams Salicylic Acid Molecular Weight Equivalent to 1 g. of Drug	
			166.08	0.83
12	Ethyl salicylate aethylis salicylas sal-ethyl salicylic ether	$\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{COO} \cdot \text{C}_2\text{H}_5$		
13	Glyceryl mono- salicylate glyceryl salicylate glycosal monosalicylic glycerinester	$\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{O} \cdot \text{C}_3\text{H}_5(\text{OH})_2$	212.09	0.65
14	Hexamethylen- amine salicylate formin salicylate methenamine salicylate saliformin	$(\text{CH}_2)_6\text{N}_4 \cdot \text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{COOH}$	278.17	0.50
15	o-Hydroxybenzyl- alcohol salicyl alcohol saligenin saligenol	$\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{OH}$	124.06	1.11
16	Lithium acetyl- salicylate hydropyrin litmopyrin tyllithin	$\text{CH}_3\text{CO} \cdot \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{COOLi}$	185.99	0.74
17	Lithium salicylate lithii salicylas	$\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{COOLi}$	143.98	0.96
18	Magnesium acetyl- salicylate apyron magisal magnespirin novacetyl	$(\text{CH}_3\text{CO} \cdot \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{COO})_2\text{Mg}$	382.43	0.72
19	Magnesium sali- cyate magnesii salicylas	$(\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{COO})_2 \cdot \text{Mg} \cdot 4\text{H}_2\text{O}$	370.46	0.75
20	Menthyl salicylate	$\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{OC}_{10}\text{H}_{19}$	276.19	0.50
21	Methoxymethyl salicylate ericin	$\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{OCH}_2 \cdot \text{OCH}_3$	182.17	0.76

TABLE 1.—Cont.

No.	Chemical, Pharmaceutical and Trade Names	Formula	Grams Salicylic Acid Molecular Equivalent to 1 g. of Weight Drug	
	mesotan salicylic acid methyl- oxymethyl ester salmester			
22	Methyl benzosali- cylate benzosalin benzoyl-salicylic acid methyl ester methyl-benzoyl salicylate	$C_6H_5 \cdot CO \cdot O \cdot C_6H_4 \cdot COO \cdot CH_3$	256.09	0.54
23	Methylene-citrylsali- cylc acid citrosalic acid novaspirin salicitrin	$CO \cdot COO \cdot CH_2 \cdot (CH_2 \cdot CO_2 \cdot C_6H_4 \cdot COOH)_2$	444.12	0.62
24	Methyl salicylate methyils salicylas oil of betula oil of gaultheria oil of sweet birch oil of teaberry oil of wintergreen	$OH \cdot C_6H_4 \cdot COO \cdot CH_3$	152.06	0.91
25	Monoglycol sali- cylate glycol salicylate glysal spirosal	$OH \cdot C_6H_4 \cdot CO \cdot OCH_2 \cdot CH_2 \cdot OH$	182.08	0.76
26	α -Naphthyl sali- cylate alphol α -naphthol salicylate	$OH \cdot C_{10}H_7 \cdot CO \cdot OC_{10}H_7$	264.09	0.52
27	β -Naphthyl sali- cylate betol naphthalol naphthosalol salinaphthol	$OH \cdot C_{10}H_7 \cdot COO \cdot C_{10}H_7$	264.09	0.52
28	Phenocoll sali- cylate salocoll	$C_2H_5O \cdot C_6H_4 \cdot NH \cdot CO \cdot CH_2 \cdot NH_2 \cdot C_7H_5O_2$	332.17	0.42

OCCURRENCE AND PROPERTIES OF SALICYLATES

13

TABLE 1.—Cont.

No.	<i>Chemical, Pharmaceutical and Trade Names</i>	<i>Formula</i>	<i>Molecular Weight</i>	<i>Grams Salicylic Acid Equivalent to 1 g. of Drug</i>
29	Phenyl acetylsalicylate acetylsalol spiroform vesipyrin	$\text{CH}_3\text{CO}\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{OC}_6\text{H}_5$	256.09	0.54
30	Phenyl salicylate phenylis salicylas phenylum salicylicum salol	$\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{COO}\cdot\text{C}_6\text{H}_5$	214.08	0.64
31	Quinine bi-salicylo-salicylate quinisal	$\text{C}_{20}\text{H}_{24}\text{O}_2\text{N}_2(\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{OC}_6\text{H}_4\cdot\text{COOH})_2$	840.36	0.66
32	Quinine salicylate chininum salicylicum quininae salicylas	$\text{C}_{20}\text{H}_{24}\text{O}_2\text{N}_2\cdot\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{COOH}\cdot\text{H}_2\text{O}$	480.27	0.29
33	Salicyl alcohol glycoside salicin	$\text{C}_9\text{H}_{11}\text{O}_6\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\text{OH}$	286.14	0.48
34	Salicylaldehyde o-hydroxybenzaldehyde salicylic aldehyde	$\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CHO}$	122.05	1.13
35	Salicylamide o-hydroxybenzamide salamid	$\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{NH}_2$	137.06	1.01
36	Salicylic acid o-hydroxybenzoic acid	$\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{COOH}$	138.05	1.00
37	Salicylsalicylic acid diplosal disalicylic acid salicyl ester of salicylic acid salicylo-salicylic acid salysal	$\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{COO}\cdot\text{C}_6\text{H}_4\cdot\text{COOH}$	258.08	1.07
38	Sodium salicylate natrium salicylicum salicylate of soda sodii salicylas	$\text{HO}\cdot\text{C}_6\text{H}_4\cdot\text{COONa}$	160.04	0.86
39	Strontium salicylate strontii salicylas strosalina	$(\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{COO})_2\text{Sr}\cdot 2\text{H}_2\text{O}$	397.74	0.69

SOLUBILITY

Salicylic acid is only slightly soluble in water, 0.18 g. being dissolved in 100 cc. at 20° C., 1.76 g. at 75° and 7.5 g. at 100°. It is readily soluble in both alcohol and ether; 39.2 g. dissolve in 100 cc. of alcohol at 15° C. and 50.5 g. in 100 cc. of ether at 15° C. The inorganic salts of salicylic acid, however, are more soluble in water than in alcohol. One hundred and eleven grams of sodium salicylate are soluble in 100 cc. of water at 15° C.; only 17 g. are soluble in alcohol at the same temperature. Other salts of salicylic acid, such as ammonium, calcium, lithium, and magnesium, are more soluble in water than in alcohol.

In contrast, the esters of salicylic acid, with the exception of hexamethylamine salicylate, are poorly soluble in water and readily soluble in alcohol. Thus some 0.3 g. of acetylsalicylic acid dissolve in 100 cc. of water at 25° C. and 20 g. in 100 cc. of alcohol. Most of the inorganic salts of acetylsalicylic acid are highly soluble in water but are rapidly decomposed in solution. Calcium acetylsalicylate is the most soluble.

Methyl salicylate is only slightly soluble in water but is infinitely soluble in alcohol and ether.

Phenyl salicylate is soluble in water only to the extent of 0.015 g. per 100 cc. at 25° C.; in alcohol 16.5 g. dissolve in 100 cc. at the same temperature.

STABILITY

Salicylic acid is stable in air but Kolbe [1880] reported that in aqueous solution (20 mg. per 100 cc.) it disappeared completely when kept in contact with wood for a year.

Sodium salicylate is affected by light (3779) and aqueous solution becomes discolored on standing. The concentration of sodium salicylate in water diminishes on standing; Hanzlik [1927] and Hanzlik and Wetzol [1920 (1480)] attribute the loss to the growth of microorganisms. Greenish and Beesley [1915] concluded from experiments that discoloration of solutions of sodium salicylate in the presence of sodium sesquicarbonate was due to the action of oxygen on the salicylate. The presence of a reducing agent such as sulfite prevents discoloration. Liberalli [1935] found that the discoloration was due to the formation of a quinoid structure of the phenolic group of the salicylate by the action of atmospheric oxygen. This change is accelerated by traces of copper and iron and by oxi-

dizing agents, microorganisms and light. The discoloration can be prevented by the addition of 0.5 per cent sodium citrate.

Acetylsalicylic acid is stable in dry air but in the presence of moisture it gradually hydrolyzes into salicylic acid and acetic acid (549, 1787). The problem of avoiding hydrolysis in prescriptions containing acetylsalicylic acid has frequently arisen (679, 1122, 1265, 1784, 2047, 4054).

Chistoni and Lapresa [1909] found that acetylsalicylic acid in water solution starts to hydrolyze in 4 hours at 18° C., in 40 minutes at 30° and in 1 minute at 100°. The hydrolysis occurs more rapidly in acid or alkaline than in neutral solution (1470, 3266).

Leech [1922] found that 50 per cent of the acetylsalicylate was hydrolyzed after 4 days in a 7.5-per-cent solution of the compound in 30-per-cent sodium citrate; 75 per cent was hydrolyzed after 9 days; and hydrolysis was complete in 17 days.

Dott [1929] found that in a 2.8-per-cent solution of sodium bicarbonate containing 3 per cent of acetylsalicylic acid 5.27 per cent of the acetylsalicylate was hydrolyzed after 4 hours and 14.14 per cent after 28 hours.

Finnemore and Gorringer [1930] reported that on the addition of water to a mixture of acetylsalicylic acid and tragacanth the hydrolysis of the acetylsalicylic acid in solution was not retarded, but hydrolysis of the undissolved particles of acid was prevented due to a protective coating of tragacanth over them.

According to Germuth [1931] the addition of a mixture of equal volumes of ethanol and glycerol to aqueous solutions of acetylsalicylic acid retarded hydrolysis of the acid. The addition of glycerin or saturation with sugar was found by Clark [1932] to have a similar effect on the hydrolysis of acetylsalicylic acid in solutions of potassium citrate. Tomski and Waller [1940] found that in a 3-per-cent solution of acetylsalicylic acid in 50-per-cent alcohol, kept under ordinary laboratory conditions, 1.5 per cent hydrolyzes in a day, 6.0 to 6.5 per cent in a week, and 13.5 to 14.5 per cent in a month.

Morton [1933] observed that the rate of hydrolysis of acetylsalicylic acid in aqueous solutions in the presence of alkali-metal citrates and acetates was independent of concentrations of the acetylsalicylic acid and alkali-metal salts but increased rapidly with a rise in temperature.

The salts of acetylsalicylic acid hydrolyze in solution much more

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Quinine and acetylsalicylic acid, which are often prescribed together for the treatment of influenza, were believed to form a poisonous substance, quinotoxine (405, 2285, 3800, 3912, 4068). Ruddiman and Lanwermyer [1924, 1926] found that such mixtures, when kept for a sufficient length of time, changed into a discolored mass. The toxicity of this product in frogs, rats, and guinea pigs was no different, however, from that of the freshly prepared mixture.

DETERMINATION OF SALICYLATE

For the estimation of salicylate in biological fluids and tissues two general methods have been used: a titrimetric method and a colorimetric method. The titrimetric method is based on the readiness with which phenolic compounds are brominated; the quantity of bromine utilized provides a measure of the amount of such compounds present. Since biological fluids frequently contain appreciable amounts of phenolic compounds other than salicylate, this method can be applied only to the estimation of salicylates separated from the other phenolic compounds. This is accomplished by extraction or steam distillation. The estimation of salicylate by bromination is much less sensitive than the colorimetric method and requires large samples of material. It has therefore been used mainly for the determination of salicylate in urine.

The colorimetric method most widely used is based on the reaction of salicylic acid with ferric chloride with the formation of a violet color even in extremely dilute solutions. Although this color reaction can be carried out directly in many biological fluids or their protein-free filtrates, it is preferable to extract the salicylic acid before applying the ferric chloride test, since mineral acids, certain neutral salts such as phosphates, tartrates, citrates and oxalates, and other substances, weaken the color reaction or suppress it entirely. The estimation of all salicylate compounds by the ferric chloride color reaction is made on the salicylic acid liberated from the compounds by hydrolysis and extraction.

ADDITIONAL REFERENCES

Stability:

92, 583, 655, 1447, 1478, 2158, 2867, 3309, 3979.

Incompatibilities:

1121, 1230, 1765, 2053, 3280, 3281, 3424, 3693, 4030.

readily than the acid itself. Acetyl-sodium-salicylate, prepared by neutralization of acetylsalicylic acid with bicarbonate, hydrolyzes overnight and becomes strongly acid (1784). Between 80 and 90 per cent of various salts of acetylsalicylic acid in 1-per-cent aqueous solution at 60° C. was found to be hydrolyzed in 10 hours (1963). The rate of hydrolysis was increasingly greater for lithium, magnesium, strontium, calcium, sodium and potassium acetylsalicylate. Thompson and Dragstedt [1933] found that calcium acetylsalicylate is readily hydrolyzed when not kept completely dry.

Hanzlik and Prescho [1925 (1472)] found that the occurrence of hydrolysis of methyl salicylate in solution depends on acidity. No hydrolysis occurs in solutions at pH 4.0 to 7.2; at pH 7.4 to 8.4 about 3 per cent is hydrolyzed in 24 hours.

Tocco [1912] found that the rate of hydrolysis of salicyl-salicylic acid in solution is increased by heat and by alkalinity of the solvent, and retarded by acidity. Hanzlik and Prescho [1925 (1471)] observed no hydrolysis of this compound in solutions at pH under 7.4. The highest degree of hydrolysis occurred at pH 8.0.

INCOMPATIBILITIES

Incompatibility of salicylic acid has been reported with compounds of bismuth (3779), iodine (283, 2272, 2960), iron (119, 283, 826, 1270, 2272, 2810, 3020), lead (283, 3020, 3779), mercury (3779), silver (2272, 3020, 3779), zinc (1877, 1978, 3779), and with ammonium carbonate (1270), antipyrine (1292, 2272, 3219, 3788, 4023), calcium hydroxide (3020), chloral hydrate (119), ethyl nitrite (283, 1270, 2421, 2810, 3820), hydrobromic acid (3786), quinine (1270, 2272, 2810, 3020), and sodium phosphate (3020). When organic or inorganic acids are added to aqueous solutions of salicylates, a precipitate of salicylic acid frequently occurs. In the presence of alkalis or on exposure to air, solutions of salicylic acid turn reddish brown (3779).

Incompatibility of acetylsalicylic acid with the following compounds has been reported: alkali hydroxides and carbonates (3779), amidopyrine (405, 3928), antipyrine (732, 2988, 3779), hexamethylenamine (405, 2988, 3779), lead acetate (2988), magnesium and iron salts (405, 3024), phenalgin (2583), phenol (2988, 3779), potassium acetate, sodium borate, sodium citrate and sodium phosphate (2988).

The Fate of Salicylates in the Body

ABSORPTION

NUMEROUS studies have been made of the absorption of salicylates by various surfaces of the body. The three general methods used in estimating the extent and rate of absorption have been: (1) measurement of the amount eliminated by the kidneys; (2) estimation of the concentration of salicylate reached in the blood; and (3) direct measurement of the amount of salicylate absorbed when known amounts are introduced into isolated cavities of the body.

The first method has been the one most frequently employed. The appearance of salicylate in the urine is a positive indication that absorption has occurred. However, quantitative estimations of the rate of absorption and of the amount absorbed cannot be made from the urinary secretion. The rate of excretion of salicylate by the kidneys bears a variable relationship to the amount in the body, and the amounts of salicylate destroyed by metabolism also show considerable variation. Some of the factors influencing these variations will be discussed later.

The appearance of salicylate in the blood is also a positive indication that the drug has been absorbed. Quantitative estimation of the concentration of salicylate attained in the blood may also serve as an indication of the relative speed of absorption. The actual extent of absorption, however, cannot be evaluated from the concentration in the blood, first, because variable amounts of salicylate are continuously metabolized and excreted, and second, because salicylate has a variable distribution in the body due to its binding with certain proteins in body fluids. Some of the factors influencing the degree of binding of salicylate, and hence the distribution of the drug in the body, will be discussed later.

In employing the third method for studying the absorption of salicylate, solutions of the drug have been introduced into closed cavities formed by ligating various parts of the gastrointestinal tract. The extent of absorption after various periods of time is then calculated from the amount of salicylate remaining in the cavity. In such studies, however, where physiological conditions

Estimation and Determination:

17, 26, 51, 78, 92, 101, 107, 139, 142, 182, 185, 191, 197, 262, 266, 333, 346, 369, 376, 393, 418, 438, 449, 460, 469, 487, 542, 586, 648, 666, 673, 677, 678, 683, 723, 774, 794, 798, 847, 848, 849, 850, 851, 860, 908, 950, 951, 979, 990, 1015, 1020, 1021, 1022, 1023, 1025, 1049, 1111, 1150, 1163, 1169, 1177, 1187, 1198, 1222, 1235, 1251, 1266, 1268, 1344, 1368, 1375, 1376, 1391, 1418, 1434, 1491, 1493, 1494, 1503, 1504, 1515, 1530, 1558, 1562, 1563, 1632, 1647, 1649, 1665, 1666, 1723, 1724, 1734, 1742, 1770, 1779, 1797, 1804, 1808, 1834, 1887, 1901, 1905, 1935, 1969, 1998, 2001, 2007, 2009, 2010, 2097, 2164, 2341, 2369, 2382, 2403, 2437, 2438, 2563, 2591, 2597, 2604, 2626, 2664, 2672, 2678, 2679, 2695, 2697, 2729, 2731, 2785, 2809, 2832, 2867, 2875, 2879, 2903, 2906, 2954, 2957, 3025, 3034, 3039, 3062, 3081, 3091, 3110, 3161, 3176, 3194, 3207, 3210, 3233, 3252, 3259, 3260, 3266, 3273, 3298, 3312, 3327, 3351, 3401, 3403, 3444, 3467, 3472, 3510, 3522, 3529, 3587, 3636, 3641, 3651, 3655, 3658, 3674, 3675, 3690, 3710, 3713, 3746, 3814, 3832, 3870, 3951.

Absorption From Various Surfaces

A. *Absorption from the oral cavity.* Bachem [1924 (120)] found traces of salicylate in the urine of 2 human subjects after washing the mouth with 2- and with 5-per-cent solutions of salicylic acid in alcohol. In an anesthetized rabbit with the esophagus ligated, 0.1 g. of salicylic acid in 2 cc. of 50-per-cent alcohol introduced into the oral cavity was followed by the appearance of salicylate in the urine 20 to 45 minutes later. Blume and Buchholz [1932], using the same technique in 15 rabbits, introduced 125 and 250 mg. of sodium salicylate into the oral cavity; salicylate appeared in the urine 25 to 56 minutes later.

B. *Absorption from the esophagus.* The absorption of sodium salicylate from the esophagus was studied by Kuzuya [1924] in rabbits. He injected 2, 3 and 5 cc. of a 10-per-cent solution of sodium salicylate into the esophagus, which was ligated at both ends; salicylate appeared in the urine 20, 40 and 15 minutes after the respective doses.

C. *Absorption from the stomach.* Early recognition that phenyl salicylate was not absorbed from the stomach but was absorbed rapidly from the small intestine led Einhorn [1888], Ewald [1889], Huber [1887], Metz [1888], Pal [1889] and Sievers and Ewald [1887] to advocate its use in human subjects for estimating, clinically, the rate of gastric emptying. The time required for the first appearance of salicylate in the urine, and in some instances the duration of its excretion after administration of 1 g. of phenyl salicylate, was used as an index of the emptying of the stomach.

Otto [1902] ligated both ends of the stomachs of animals, introduced solutions of sodium salicylate, and tested the urine for salicylate. One hour after 3 cc. of a 5-per-cent solution was given to a guinea pig and 5 cc. of the same solution to a rabbit, the urine contained salicylate. However, in two cats, one of which received 6 cc. of a 5-per-cent solution and the other 5 cc. of a 10-per-cent solution, and in a dog which received 10 cc. of a 10-per-cent solution, no salicylate appeared in the urine.

Burow [1911] administered 0.5 g. of various salicylates (salicylic acid, sodium salicylate, acetylsalicylic acid, lithium acetylsalicylate, phenyl salicylate, antipyrine salicylate and phenetsal) by stomach tube to a dog with a duodenal fistula. From qualitative

may have been altered by ligature, anesthesia and surgical manipulations, a question may be raised as to the influence of these upon the normal absorption.

The first observations that absorption starts within a short time after the ingestion of salicylates were based on the appearance of salicylate in the urine of men 10 minutes after they had ingested 4 g. of salicylic acid. Ingria [1886] observed a positive test for salicylate in the urine of five patients 22 to 24 minutes after they were given 0.25 g. of salicylic acid. Einhorn [1888] and Decker [1889] reported that salicylate was present in the urine 45 to 75 minutes after ingestion of phenyl salicylate. The appearance of salicylate in the urine 20 to 38 minutes after oral administration of 1 g. of acetylsalicylic acid to each of five patients was reported by Hill [1902]. Thelen [1909] gave 1 g. of acetylsalicylic acid to a group of normal individuals; salicylate first appeared in the urine after 15 to 20 minutes, reached a maximum at 12 hours, and was absent after 18 hours.

Pinczower [1910] measured the time required for the first appearance of salicylate in the urine after administration of 1 g. of salicylic acid or equivalent doses of other salicylates. The data reported by him are shown in Table 2.

TABLE 2.—*Time Required for First Appearance of Salicylate in Urine**

<i>Drug</i>	<i>No. of Subjects</i>	<i>Average Time (min.)</i>
Salicylic acid	7	10
Sodium salicylate	5	10-15
Acetylsalicylic acid	5	10
Methylene-citrylsalicylic acid	6	10-15
Phenyl salicylate	4	20
Antipyrine salicylate	3	25

*Data of Pinczower (2744).

Further evidence of the rapid onset of absorption is given by the appearance of salicylate in the blood soon after ingestion. Fiessinger and Debray [1922] found from 4 to 5 mg. per 100 cc. of serum in human subjects 10 minutes after administering 1 g. of sodium salicylate. Blume and Nohara [1933] found salicylate in the blood $1\frac{1}{2}$ minutes after oral administration of 0.25 g. of sodium salicylate to rabbits.

tinal absorption in 30 minutes were, respectively, 72.8, 55.6 and 47.2 per cent.

E. *Absorption from the large intestine.* Fiedler [1905] administered 4 to 5 g. of sodium salicylate in 250 cc. of water to men by enema. Two to 5 hours later a cleansing enema of 1 quart of water was given and the unabsorbed salicylate in the fluid passed was determined by analysis. He found that at 2 hours an average of 65 per cent was absorbed and at 5 hours 92 per cent. Massol and Minet [1908] in five similar experiments found that only 24 per cent of the drug had been absorbed 5½ hours after rectal administration.

Blume and Nohara [1933] compared the absorption of sodium salicylate in rabbits after administration by mouth and by rectum. Absorption was judged by the concentration of salicylate in the blood and the amount excreted in the urine. One hour after 0.25 g. of sodium salicylate was given by enema, the blood contained 8.5 mg. of salicylate per 100 cc. and after administration by stomach tube, only 6.0 mg. per 100 cc. One and one-half hours after the enema 44 mg. of salicylate had been eliminated by the kidneys and only 15.5 mg. after administration by stomach tube. It may be concluded from these experiments that absorption of sodium salicylate in the rabbit is more rapid from the large intestine than from the upper gastrointestinal tract.

Griffith, Leake and Butt [1945] concluded from their experience in the Navy Rheumatic Fever Unit at Corona, California, that in man, contrary to rabbits as found by Blume and Nohara, salicylates are absorbed poorly from the rectum.

F. *Absorption from the vagina.* Fehling [1875] (as cited by Hanzlik [1927]), reported that salicylic acid could be found constantly in the urine when daily vaginal douches of 0.1- to 0.165-per-cent salicylic acid solutions were used. Absorption from the vagina was the cause of death in one case observed by Vleurinck [1933]. He reported further that in Southern Rhodesia women attempting to commit suicide stuff their vaginas with a plant containing methyl salicylate.

G. *Absorption from the urinary bladder.* Lenko and Krzyzanowski [1924] found that sodium salicylate is absorbed from the bladder of the dog. When the bladder was filled with a 5-per-cent solution a positive salicylate reaction was obtained in the ureteral urine after 25 minutes.

tests for salicylate made on the fluid from the fistula he concluded that soluble salicylates are readily absorbed from the stomach, whereas insoluble salicylates pass through the stomach and are hydrolyzed in and absorbed from the small intestine.

In the urine of a dog with a ligated cardia and pylorus Tocco [1912] found no salicylate 50 minutes after introducing 1 g. of salicylsalicylic acid into the stomach, but did find some after the passage of an additional hour.

After ligating the cardia and pylorus in 16 anesthetized cats, Carnot, Papaconstantinou and Simonnet [1932] injected 0.5 g. of sodium salicylate in 10-per-cent solution into the stomach. The salicylate in the blood serum and urine was estimated by Hérissé's method (1563). Absorption occurred only when the stomach contents were acid, not when they were neutral or alkaline. Absorption was more rapid in young animals, or after injection of histamine. Injection of sodium bicarbonate into the stomach interrupted absorption of the salicylate, and introduction of hydrochloric acid caused its resumption.

Bradley, Schnedorf and Ivy [1936] studied the absorption of salicylates from the stomach and intestines of anesthetized dogs with the pylorus ligated. The drug was introduced into the stomach by cannula. An hour later the gastric contents were analyzed for salicylate. After 383 mg. of salicylic acid an average of 63.9 per cent disappeared from the stomach in 1 hour. After equivalent doses of sodium salicylate, calcium salicylate and acetylsalicylic acid, the portions that disappeared in 1 hour were, respectively, 43.3, 47.1 and 48.9 per cent. These investigators attributed the differences in absorption of these compounds to their molecular size and the pH of the medium in which they are dissolved. In unanesthetized dogs given acetylsalicylic acid, an average of 68.6 per cent was absorbed in 1 hour. This finding suggests the importance of the question raised at the beginning of this chapter as to the effect of disturbances of physiological conditions upon absorption.

D. *Absorption from the small intestine.* Bradley, Schnedorf and Ivy [1936] measured the absorption of salicylates from an isolated loop of dog intestine 24 inches in length. Thirty minutes after introduction of the drug into the loop the contents were analyzed for salicylate. After 383 mg. of salicylic acid, 59.6 per cent was absorbed in 30 minutes. After equivalent amounts of sodium salicylate, calcium salicylate and acetylsalicylic acid, the values for the intes-

Juhl [1884] sprayed the human leg with a 2-per-cent solution of salicylic acid and sodium salicylate in alcohol and found salicylate in the urine. Ritter [1884] found salicylate in the urine after application to the skin of four individuals of salicylic acid and sodium salicylate in alcoholic solution and in ointment.

In a number of human subjects Ingria [1886] demonstrated that salicylic acid dissolved in oil of sweet almond was absorbed from the skin; salicylate appeared in the urine 3 to 5½ hours after application of amounts as small as 0.25 g. This investigator concluded that absorption is proportional to the amount applied, the duration of contact, and the condition of the skin.

Bourget [1893] applied various salicylic acid ointments to different areas of skin of men and women and determined the salicylate in the urine. The ointment bases used were glycerin, vaseline, axungia, and a mixture of lanolin, oil of turpentine and axungia. Absorption was most rapid and complete after using the mixture; salicylate first appeared in the urine ½ hour after application and reached a maximum after 1 hour. From urines collected for 24 hours, 0.2 to 1.4 g. of the salicylic acid were recovered after the application of 10 g. Absorption was found to be most rapid in young adults, more complete in women than in men, and more complete from the region of the joints than from the back.

Linossier and Lannois [1896 (2162)] found that when 2 g. of methyl salicylate were applied, in a dressing, to the limb of a normal individual, about 10 per cent appeared in the urine and when 4 g. were applied, 25 to 35 per cent appeared in the urine. They also found that a significant fraction of the absorbed salicylate is eliminated in the feces.

Vogel [1899] found salicylate in the urine ¾ of an hour after 2 g. of salicylic acid in the form of an ointment had been rubbed on his skin.

Dreser [1903] applied 2 g. of methyl salicylate, and on another occasion 2 g. of amyl salicylate, to the skin of two rabbits. With the methyl compound, the first appearance of salicylate in the urine occurred after 1 hour; with the amyl, after 24 hours.

After application to the skin of human subjects of 10 g. of glyceryl salicylate, methoxymethyl salicylate, or a soap salve containing 10 per cent of salicylic acid, Zeigan [1903] found salicylate in the urine.

Schwenkenbecher [1904] immersed mice in a saturated aqueous

According to Blume and Fischer [1935] a 2.5-per-cent sodium salicylate solution is not absorbed by the normal bladder of rabbits. But the inflamed mucosa of the bladder is able to absorb large amounts of such a solution, the absorption depending on the degree of inflammation.

H. *Absorption from the respiratory tract.* Planclies [1924] obtained a positive salicylate test in urine after the smoking of 0.25 g. of sodium salicylate or salicylic acid in the form of cigarettes impregnated with this drug.

Blume and Breunig [1931] gave 10 cc. of a 2.5-per-cent solution of sodium salicylate to rabbits by intratracheal injection; salicylate appeared in the urine after 2 to 12 minutes.

I. *Absorption after parenteral injection.* Blume and Breunig [1931] found salicylate in the urine of rabbits 12 to 26 minutes after they were given 10 cc. of a 2.5-per-cent solution of sodium salicylate by subcutaneous injection.

Blume and Fischer [1935], after giving 10 cc. of a 2.5-per-cent solution of sodium salicylate to rabbits by intramuscular injection, found first traces of salicylate in the blood after 1 to 2 minutes, and the highest concentration after 1 hour; the urinary elimination of salicylate started after 30 minutes, and in 24 hours an average of 70 per cent of the salicylate was eliminated. Thirty minutes after the injection, the concentration in the blood was one and one-half times that found after rectal administration of the same dose.

Blume and Plum [1935] compared the absorption of sodium salicylate in rabbits after intraperitoneal and intrapleural administration of 250 mg. of the drug. The average maximum concentration of salicylate in the blood in 12 animals after intraperitoneal administration was 0.135 mg. per cc. and occurred in 30 minutes; the average concentration in 12 animals after intrapleural administration was 0.150 mg. per cc. and occurred in 1 hour.

J. *Absorption from the skin.* It has been demonstrated by numerous investigators that salicylates applied to the skin are absorbed, as judged from their appearance in the blood, urine and feces. Although Kolbe [1875 (1925)] found no salicylate in the urine of men after their immersion in water containing 0.1 per cent of salicylic acid, Beyer [1880] found that immersion for 20 minutes in a bath (no volume stated) at 70° F. in which 3 oz. of salicylic acid had been dissolved, resulted in the appearance of traces of salicylate in the urine.

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tis) symptoms of salicylate poisoning were observed after 100 g. of a 40-per-cent salicylic acid ointment were applied as a plaster to the skin of a leg for about 18 hours. A third girl, aged 16, severely ill with otitis, lupus vulgaris of the face and arm, elephantiasis of one leg and tuberculosis of one foot, died 21 hours after 200 g. of the same ointment had been applied similarly to one leg. The symptoms were typical of salicylate poisoning.*

Von Bonsdorff, Tallqvist and Therman [1924] found that the cutaneous absorption of salicylate from a mixture of 10 parts of salicylic acid and 100 parts of vaseline or animal fat was almost four times as great as from a mixture of equal parts of salicylic acid in oil of turpentine.

After applying salicylic acid in various vehicles to the unbroken skin of 62 patients Leslie-Roberts [1928] found salicylate in the urine of 48.

From experiments with patients Moncorps [1929, 1931] concluded that the cutaneous absorption of salicylic acid depends on the chemical characteristics of the drug. In experiments with rabbits Kionka [1931] determined the minimum amounts of various salicylates, applied to the skin in different vehicles, which were necessary to obtain the appearance of salicylate in the urine; he concluded that the various salicylates and the different ointment bases showed little difference.

Merz [1931] rubbed potassium, sodium and lithium salicylate in various ointment bases into the skin of rabbits. He found that the amounts of salicylate eliminated in the urine in 24 hours indicated that absorption varied both with the amount of the drug applied and the nature of the ointment base.

Eimer [1933] immersed mice in aqueous solutions of salicylic acid, phenyl salicylate and antipyrine salicylate, and from the amounts of salicylate in the urine concluded that absorption is increased when carbon dioxide is bubbled through the bath solution.

Benzinger and Wyrsh [1933] applied 1 g. of salicylic acid as a 10-per-cent ointment to the skin of men and recovered 1 per cent of the salicylate in the urine in 24 hours.

Gehlen and Blankenstein [1934] found salicylate in the blood of seven people who had been massaged with 10 g. of an ointment containing 16 per cent of boric glycerin salicyl esters. The concen-

*See also two cases of fatal salicylate poisoning reported by Kalbe [1923].

solution of salicylic acid and in 2- and 5-per-cent solutions of sodium salicylate and found salicylate present in the urine in all instances.

Gundorow [1904] applied various salicylic acid ointments to the skin of men and dogs and found that salicylate was absorbed even when the ointment was not rubbed in. Impens [1907], after applying equivalent amounts of various salicylate esters to the skin of man, obtained the following recoveries from urine: amyl salicylate, 2.6 per cent; methoxymethyl salicylate, 7.6 per cent; methyl salicylate, 9.4 per cent; and glycol-monosalicylate, 15.9 per cent.

Lehmann [1908] obtained more rapid cutaneous absorption of glycol-monosalicylate on mixing it with an equal part of alcohol.

Thelen [1909] applied equal and repeated doses of various salicylate esters to the skin of healthy individuals. The compounds applied were salicyl-iodine soap, methoxymethyl salicylate, salicylate vaseline preparation, salicylic acid soap, ethylglycolic acid ester of salicylic acid, and bornyl salicylate. The number of applications required before the first appearance of salicylate in the urine was observed; these were two, three, four, five and six applications, respectively, for each compound used except bornyl salicylate; no salicylate appeared in the urine after the seventh application of this substance.

Sauerland [1912 (3039)] determined the amount of salicylate excreted in the urine of men 24 hours after the cutaneous application of 750 mg. of three salicylate esters in 3 g. of three different ointment bases. The findings are given in Table 3, and it will be seen that the base used has a marked influence on absorption.

TABLE 3.—*Urinary Excretion of Salicylate after Cutaneous Application of 750 mg. in Various Ointment Bases**

<i>Drug</i>	<i>Adeps Suillae</i>	<i>Vaseline</i>	<i>Adeps Lanae</i>
	(MILLIGRAMS SALICYLATE EXCRETED IN URINE)		
Methyl salicylate	2.70	3.37	0.67
Glycol-monosalicylate	0.91	65.99	87.17
o-Oxybenzyl alcohol	19.40	1.54	

*Data of Sauerland (3039).

Lenartowicz [1914] applied 10-, 15- and 20-per-cent salicylic acid ointment to the skin of normal individuals and found salicylate in the urine. He reported three cases of salicylate poisoning due to absorption through the skin. In two girls 22 years of age (one with extensive lupus vulgaris and the other with gonorrheal arthri-

oxide and hydrochloric acid on the absorption of acetylsalicylic acid. Their findings are shown in Table 4.

Table 5 shows the proportion of these drugs absorbed from the ligated intestines of dogs at various times after administration.

TABLE 4.—*Effect of pH and Molecular Size upon Absorption of Salicylate from the Ligated Stomach and Intestine**

Equivalent of 383 mg. Salicylic Acid Administered	pH	Molecular Weight	Per cent Absorption (1 hr.)	Per cent Absorption from Intestine (30 min.)
Salicylic acid	2.5	138	63.9	59.4
Sodium salicylate	6.8	160	43.3	72.8
Calcium salicylate	6.1	350	47.1	58.3
Acetylsalicylic acid	2.9	180	48.9	47.1
Acetylsalicylic acid + calcium gluconate	3.5		48.3	50.7
Acetylsalicylic acid + sodium bicarbonate	7.3		27.7	44.4
Acetylsalicylic acid + magnesium oxide	9.0		19.0	47.9
Acetylsalicylic acid + hydrochloric acid	1.7		58.1	
Acetylsalicylic acid + hydrochloric acid	1.25		57.1	

TABLE 5.—*Percentage of Salicylates Absorbed from the Ligated Intestine**

	MINUTES AFTER ADMINISTRATION				
	15	30	45	60	75
Salicylic acid	46.1	59.6	66.3	71.9	80.9
Sodium salicylate	40.7	72.8			
Calcium salicylate		58.3			
Acetylsalicylic acid	18.4	47.1	59.1	63.4	76.9
Acetylsalicylic acid + calcium gluconate	23.4	50.7	59.8	65.9	76.1
Acetylsalicylic acid + sodium bicarbonate	16.8	44.4	48.5	65.2	75.3
Acetylsalicylic acid + magnesium oxide		47.9			

*Data of Bradley, Schnedorf and Ivy (419).

The investigators concluded that the rate of absorption from the stomach is more rapid with the smaller salicylate molecules and at a low pH. Calcium gluconate, which does not materially affect the pH of the acetylsalicylic acid solution, does not affect the rate of gastric absorption. Sodium bicarbonate and magnesium

tration of salicylate in the blood varied between 1.57 and 7.5 mg. per 100 cc.

Brown and Scott [1934 (456)] found that the cutaneous absorption of methyl salicylate in man was increased by dissolving the drug in alcohol, liquid petrolatum or anhydrous lanolin, and by suspension in water. Additional factors increasing absorption were higher temperature and massage. These investigators (457) also compared the extent of absorption of several salicylate esters and found a decreasing order of absorption of glycol-monosalicylate, methyl salicylate, methoxymethyl salicylate, ethyl salicylate, propyl salicylate, butyl salicylate and amyl salicylate.

Beutner and his associates [1943] found that the cutaneous absorption of methyl salicylate from an ointment is increased by the addition of menthol.

Cogen and Hirsch [1944] found that salicylic acid penetrates the excised cornea but that the salts of salicylic acid do so only after the epithelium has been removed. The authors attribute this difference to the difference in solubility of the acid and its salts in fats, believing that substances penetrate the epithelium only insofar as they are soluble in fat.

From the observations cited here, there can be no doubt that salicylates are absorbed from the skin. The speed of absorption depends on a number of factors for which there is less uniformity of findings, such as the compound used, the vehicle, and the condition of the skin—i.e., rubefaction after massage or chemical irritation.

Factors Influencing Absorption From Alimentary Tract

Several conditions, such as molecular size, degree of hydrolysis and the nature of the solvent, have been suggested as significant factors in the speed of absorption of salicylates from the gastrointestinal tract.

Breguet [1912] found no marked difference in absorption of sodium salicylate from an aqueous and from a 20-per-cent alcohol solution given to rabbits with ligated pylorus.

Bradley, Schnedorf and Ivy [1936], in experiments on dogs with ligated stomachs and isolated intestinal loops, studied the speed of absorption of equivalent amounts of various salicylates and the influence of calcium gluconate, sodium bicarbonate, magnesium

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emptying of the gastric contents into the small intestine where the salicylate is more rapidly absorbed.

Hydrolysis of Salicylate Esters in Gastrointestinal Tract

Whether the esters of salicylic acid are hydrolyzed prior to absorption and, if so, where the site of hydrolysis in the gastrointestinal tract is, have been the subject of some study. In 1885 von Nencki (2548) synthesized phenyl salicylate and showed that it passes through the stomach unchanged but is split into phenol and salicylic acid by the pancreatic juice. It has consequently been used as an enteric coating for pills (1257, 2606, 3293). Marshall and Bauer [1943] studied the hydrolysis of phenyl salicylate *in vitro* and found that it occurs only if the pH is above 8.2 and thus only in the intestinal tract below the duodenum.

Hanzlik and Prescho [1925 (1471)] found that gastric juice does not hydrolyze salicylsalicylic acid *in vitro*, nor do buffer solutions between pH 4.0 and 7.4. In alkaline buffer solutions, however, there is some hydrolysis, which suggests that it can occur in the intestinal fluids.

From experiments with animals and men, Hanzlik and Wetzel [1920 (1481)] and Hanzlik and Prescho [1925 (1472)] concluded that methyl salicylate is partly hydrolyzed and partly absorbed unchanged.

Vinci and Curro [1909] found that methylene citrylsalicylic acid is completely hydrolyzed in the gastrointestinal tract.

The hydrolysis of acetylsalicylic acid in the gastrointestinal tract was first studied by Floeckinger [1899]. He administered 250 mg. per kg. to guinea pigs and 35 minutes later found no free salicylate in the stomach or intestines; after 2 to 3 hours he found only a trace of free salicylate in the gastric contents but a large amount in the intestines. He concluded that acetylsalicylic acid is hydrolyzed only in the intestines. From *in vitro* studies, Dreser [1899] and Gazert [1900] came to a similar conclusion. Dreser found no salicylic acid after 1 hour in a 1-per-cent solution of acetylsalicylic acid in 0.2 per cent hydrochloric acid. In an alkaline solution, however, hydrolysis started in 10 minutes. Gazert observed no hydrolysis of acetylsalicylic acid in normal gastric juice containing 0.18 per cent hydrochloric acid.

Bondi and Katz [1911] found that *in vitro* at 37° C. acetylsalicylic acid is hydrolyzed slowly in bicarbonate solution and in

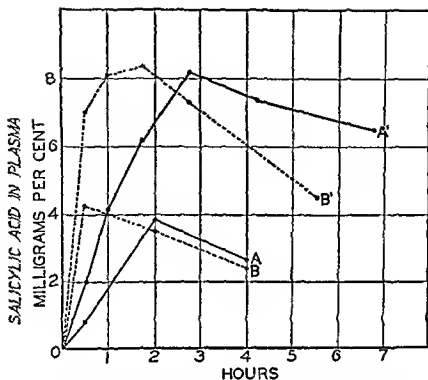


FIGURE 3.—Influence of sodium bicarbonate on the salicylic acid content of plasma. *A*, 0.65 g. acetylsalicylic acid; *A'*, 1.30 g. acetylsalicylic acid; *B*, 0.65 g. acetylsalicylic acid with 1 g. NaHCO_3 ; *B'*, 1.30 g. acetylsalicylic acid with 2 g. NaHCO_3 . Reproduced from Lester, Lolli and Greenberg (2103).

oxide, which raise the pH of the solution, inhibit the rate of gastric absorption. The rate of intestinal absorption is much less affected by the pH of the solution; the addition of calcium gluconate, sodium bicarbonate or magnesium oxide does not markedly change the intestinal absorption of acetylsalicylic acid.

Lester, Lolli and Greenberg [1946] found that sodium bicarbonate hastens the absorption of acetylsalicylic acid given orally to normal individuals. Curves *A* and *A'* in Figure 3 show concentrations of salicylate in plasma after administration of 0.65 and 1.30 g. of acetylsalicylic acid. *B* and *B'* are similar curves obtained when sodium bicarbonate was given simultaneously with the acetylsalicylic acid. The bicarbonate did not appreciably change the maximum concentration of salicylate reached in the plasma but the maximum was reached appreciably sooner. This effect is attributed by the investigators to the fact that the bicarbonate causes a quicker

cylate depends for its therapeutic action on the development of an effective concentration in the body. Considerable study has been made of the influence of dose, mode of administration, absorption, distribution within the body, and metabolism and excretion, on the concentrations developed, particularly in the blood.

Concentration of Salicylate in Blood and Plasma

Levin [1912] gave sodium salicylate to goats by stomach tube and by subcutaneous and intramuscular injections. Concentrations of salicylate in the serum were determined by a method which the author states does not give the true value for total salicylate but can be used for relative values. The amount of sodium salicylate given, the maximum concentrations reached in the serum, the times at which they were reached, and the time of disappearance of the salicylate from the serum, are shown in Table 6. It is of note that after 50 g. of salicylate subcutaneously the concentration in the serum remained at a maximum level for 18 hours.

TABLE 6.—*Salicylate in Serum of Goats Following Administration of Sodium Salicylate by Various Routes**

	Subcu- taneous, 25 g.	Intramus- cular, 25 g.	Subcu- taneous, 50 g.	Stomach Tube, 25 g.
Time of maximum concentration	2-4 hr.	2-4 hr.	4-22 hr.	1-4 hr.
Maximum concentration, mg. per 100 cc.	21	55.6	55.6	26
Time for disappearance from serum	22 hr.	32 hr.	†	46 hr.

*Data of Levin (2111). †Died after 23 hours.

Friderichsen [1917] gave 2 g. of sodium salicylate per kg. to a rabbit orally. The concentrations in the blood after 35, 65, 95, 120 and 128 minutes were 37, 72, 90, 104, and 133 mg. per 100 cc. respectively. Another rabbit, 1, 2, 5 and 24 hours after receiving 1.67 g. per kg. orally, had concentrations of salicylate in the blood of 46, 65, 78 and 65 mg. per 100 cc.

Blume and Breunig [1931] described a typical blood salicylate curve found in rabbits given 125 mg. of sodium salicylate per kg. subcutaneously. After 10, 15, 30, 60 and 180 minutes, the respective concentrations were 0.7, 1.8, 2.5, 2.7 and 0 mg. per 100 cc.

mixtures of trypsin and bile. They concluded that acetylsalicylic acid may be present in the intestinal tract for a considerable length of time and is absorbed in part unhydrolyzed. Chambers [1912] observed that acetylsalicylic acid is hydrolyzed very slowly in water, in 1 per cent sodium bicarbonate, and in 0.2 per cent hydrochloric acid. He concluded that it is absorbed largely unchanged.

The hydrolysis of acetylsalicylic acid in buffer solutions at body temperature was studied by Hanzlik and Presho [1923] and Hanzlik [1927]. They found that hydrolysis is most rapid at the acidity corresponding to that of gastric juice and at the alkalinity of the intestinal juice, but is slight in the vicinity of neutrality. Contrary to most investigators, they concluded that the hydrolysis of acetylsalicylic acid occurs in the stomach.

As a result of the conflicting experimental data presented in the literature a variety of opinions has been expressed in textbooks regarding both the extent and the site of hydrolysis of acetylsalicylic acid in the gastrointestinal tract. With regard to the extent of hydrolysis, Faddis and Hayman [1943], as well as Dalmady [1923 (801)], state that acetylsalicylic acid is not hydrolyzed but is absorbed unchanged. Cushny [1936] states that it is partly hydrolyzed but that some is absorbed unchanged. Dilling [1941] expresses the opinion that some acetylsalicylic acid is hydrolyzed but that most of it is absorbed as sodium acetylsalicylate.

Concerning the site of hydrolysis of acetylsalicylic acid, it is accepted in most textbooks that this occurs in the alkaline medium of the small intestines (123, 796, 893, 1616, 1905, 2078, 2330, 2422, 3083, 3255). Only Davison [1944] states that acetylsalicylic acid is hydrolyzed in both the stomach and the intestines.

The preponderance of data and opinion in the literature thus indicates that the esters of salicylic acid are hydrolyzed to some extent in the gastrointestinal tract, mainly in the small intestines. Concerning the extent of hydrolysis there is considerably less unanimity. That it is not complete and that at least part of the unhydrolyzed compound may be absorbed are further suggested by the reported observations of unchanged esters in the blood and urine following their ingestion, observations which will be discussed more fully later.

CONCENTRATIONS IN BODY FLUIDS AND TISSUES

Although the mechanism of the action of salicylate is not known the fact remains that, as with most drugs given systemically, sali-

salicylic acid (average 13.0 g.) had concentrations in the blood of 18 to 35 (average 26.5) mg. per 100 cc. Fourteen rheumatics receiving the equivalent of 4.5 to 17.0 g. of salicylic acid (average 12.5 g.) had concentrations of 14 to 31 (average 21) mg. per 100 cc. The investigators concluded that there was a tendency for the concentration of salicylate in the blood to be lower in rheumatic than in nonrheumatic individuals. The blood was taken for analysis, from each subject, when toxic symptoms occurred; the times were highly variable. Since there is no evidence that at the time of taking the blood sample from each subject the concentration had reached its maximum value, the conclusion as to the differences in maximum concentrations attained is open to doubt.

Fiessinger and Debray [1922] gave 1 g. of sodium salicylate to human subjects and determined the concentration of salicylate in the serum at various intervals. After 10, 20 and 30 minutes and 1 to 1½, 5, 12 and 18 hours, the concentrations were approximately 4.5, 5.5, 5.5, 10, 6, 4 and 1 mg. per 100 cc. respectively, and after doses of 0.25 and 0.5 g. the concentrations in 1½ hours were 1 to 2 and 5 to 6 mg. per 100 cc. of serum.

Taltavull and Maurelli [1943] found higher concentrations of salicylate in the blood of human subjects when 15 g. of sodium salicylate were given rectally than when given orally. The average values for concentrations of salicylate were, respectively, 49.6 and 10.1 mg. per 100 cc. of blood after 2 hours, and 45.6 and 4.6 after 10 hours. The concentrations of salicylate reported in the blood by these investigators after oral administration of 15 g. of sodium salicylate are so small as to make their validity doubtful.

The investigations of Coburn [1943] on patients having rheumatic fever gave considerable therapeutic importance to the study of the concentrations of salicylate in blood and plasma. He determined the concentrations reached in the plasma in effective therapy and suggested a concentration of salicylate in the plasma of approximately 40 mg. per 100 cc. as the minimum for effective action. In a group of 10 rheumatic patients, each receiving 10 g. of sodium salicylate daily for 3 days, the concentrations in the plasma on the fourth day ranged between 29.5 and 52.0 mg. per 100 cc. Forty-four rheumatic patients received sodium salicylate in daily doses of 0.1 to 0.19 g. per kg. The concentration of salicylate in the plasma for each of the daily dosages is shown in Figure 5. It is apparent that a poor correlation exists between the dose and the

of blood. These low concentrations are not in accord with the findings of most investigators of the subject.

In experiments with rabbits, Blume and Nohara [1933] determined concentrations of salicylate in the blood after administration of 0.25 g. of sodium salicylate by stomach tube and by enema. The average blood curves charted from their report (see Figure 4) show that administration by stomach tube results in a maximum concentration of 8.4 mg. per 100 cc. of blood in 3 hours; and rectal administration, a maximum concentration of 9.0 mg. per 100 cc. in 1 hour. As noted in Chapter II, absorption after rectal administration is, in rabbits, more rapid than after oral administration.

A large part of the data in the literature concerning the concentrations of salicylate in blood and plasma in human beings was obtained in connection with the therapy of rheumatic fever. The amounts of salicylate given in these studies were, therefore, often large and administration was repeated.

Scott, Thoburn and Hanzlik [1917] compared the concentrations of salicylate in the blood of rheumatic to that in nonrheumatic individuals after the administration of sodium salicylate. Nine non-rheumatic subjects receiving the equivalent of 9.0 to 19.36 g. of

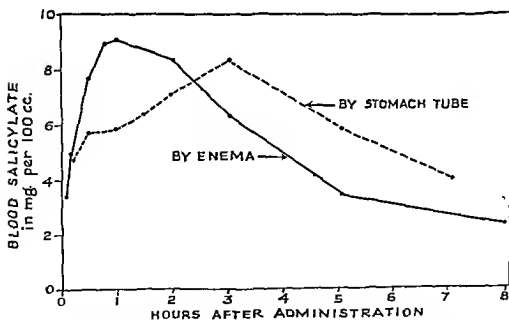


FIGURE 4.—Concentration of salicylate in blood of rabbits after 0.25 g. of sodium salicylate. Based on data of Blume and Nohara (336).

The concentration of salicylate in the plasma of rheumatic children was investigated by Lawson [1944], who administered sodium salicylate to 11 children and acetylsalicylic acid to 4. A poor correlation was found between the dosage of salicylate and the concentration in the plasma. It is difficult to draw conclusions from these observations, since 9 of the children also received varying amounts of sodium bicarbonate and 2 received magnesium carbonate, which may affect absorption and elimination.

Fashena and Walker [1944] found that initial doses of 0.22 and 0.23 g. of salicylate per kg. were necessary to attain concentrations of salicylate in the blood of about 35 mg. per 100 cc. in two children. (In both of these children, tinnitus and vomiting developed within 24 hours.) This concentration could then be maintained with daily doses of 0.15 and 0.17 g. per kg. Daily doses of 0.15 g. per kg. given to two other children, without a high initial dose, were insufficient to attain such concentrations.

Smith [1945 (3272)] gave sodium salicylate in doses of 2 g. to normal individuals and determined the concentration of salicylate in the plasma of each at some time between 1 and 8 hours after administration. From the distribution of the values found he obtained the curve shown in Figure 6. He concluded that the absorp-

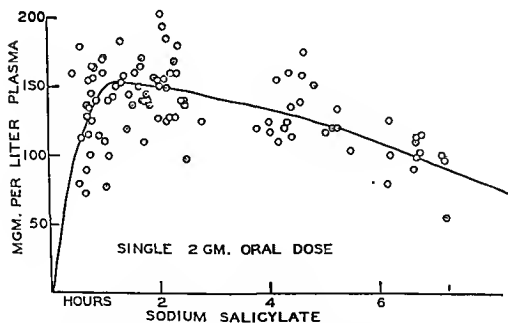


FIGURE 6.—Concentration of salicylate in plasma after single oral doses of 2 g. of sodium salicylate. Reproduced from Smith (3272).

concentration. As a result, Coburn suggested determinations of salicylate in blood or plasma as a guide in adjusting the dosage of salicylate in rheumatic fever therapy. Coburn found that 48 hours after discontinuance of salicylate therapy, in 9 out of 10 patients who had been maintained at concentrations of salicylate in the plasma of 27.2 to 40.5 mg. per 100 cc., no salicylate remained in the plasma.

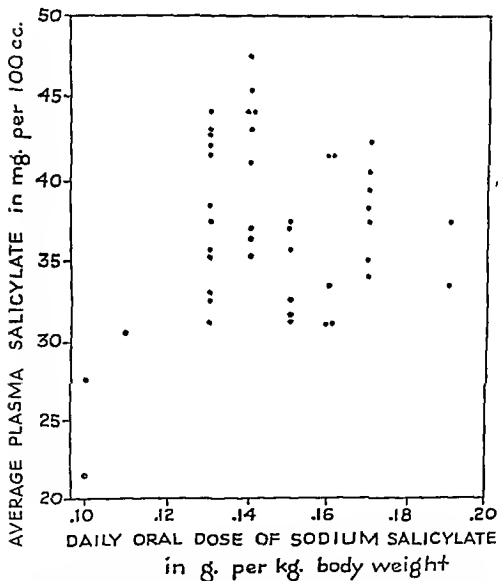


FIGURE 5.—Concentration of salicylate in plasma of 44 patients maintained with daily oral doses of 10 g. of sodium salicylate. Based on data of Coburn (696).

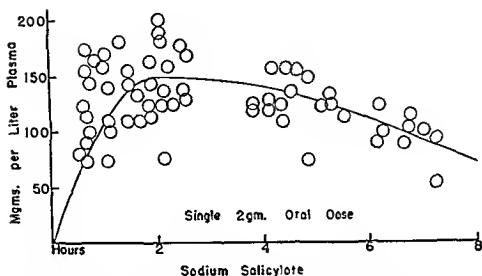


FIGURE 7.—Concentrations of salicylate in plasma after single 2-g. doses of sodium salicylate given to normal adults. Reproduced from Smith, Gleason, Stoll and Orgorzalek (3274).

cyrate, and that this maximum is reached later and is maintained for a number of hours, is explained by the investigators as due to slower, more prolonged absorption.

The concentrations of salicylate in plasma were determined after multiple doses of various salicylates. Convalescent patients each

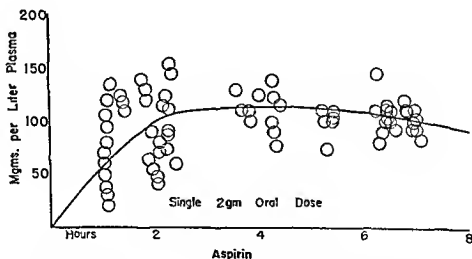


FIGURE 8.—Concentrations of free salicylate in plasma after single 2-g. doses of acetylsalicylic acid. Reproduced from Smith, Gleason, Stoll and Orgorzalek (3274).

tion of sodium salicylate after oral administration is rapid and that the maximum concentration in the blood occurs about 1 hour after ingestion.

McEachern [1945] studied the rate of disappearance of salicylate from the plasma of rheumatic patients given single doses of sodium salicylate. When a dose of 20 g. was given intravenously to 6 patients, the average concentrations of salicylate in the plasma at 1, 6, 12 and 24 hours were 57, 42, 35 and 27 mg. per 100 cc. respectively. In 13 patients, following intravenous injection of 10 g. of sodium salicylate, the average concentrations of salicylate in the plasma at the same intervals were 36.5, 31.4, 22.6 and 15.5 mg. per 100 cc. After oral administration of 10 g. of sodium salicylate to 6 patients the average concentration of salicylate in the plasma rose slowly from a level of 5.0 mg. per 100 cc. in 1 hour to a maximum of 18.5 mg. per 100 cc. in 12 hours. Absorption was presumably complete at this time and the concentration diminished during the next 12 hours to a level of 14 mg. per 100 cc. The curve during the last 12 hours roughly coincided with that occurring at the same time after intravenous injection of 10 g. of sodium salicylate.

Keith and Ross [1945] determined the concentrations of salicylate in the plasma of rheumatic patients receiving daily doses of salicylate. The determinations were always made 9 hours after the salicylate was given. The concentration reached each day did not vary greatly in the individual patients. In 19 receiving 13.3 g. of sodium salicylate daily the concentrations of salicylate in the plasma ranged between 24 and 39 mg. per 100 cc., with an average of 31. In 12 patients receiving 10 g. of sodium salicylate daily the concentrations ranged between 19 and 37 mg. per 100 cc., with an average of 27.

Smith and his associates [1946 (3274)] determined the concentrations of salicylate in the plasma of normal subjects after single 2-g. doses of sodium salicylate or acetylsalicylate. The concentration of salicylate in the plasma was determined in each of the subjects between 1 and 8 hours after administration. The distribution of the values found for each of the drugs and the curves drawn through them by the investigators are shown in Figures 7 and 8. The curve for the sodium salicylate is presumably the same one described by Smith [1945 (3272)] in a previous publication. The fact that after the acetylsalicylate the maximum concentration of salicylate reached in the plasma is lower than after sodium sali-

tration of 0.65 and 1.30 g. to an individual weighing 75 kg. These investigators demonstrated also that in human subjects the unchanged acetylsalicylate is present in the plasma for a short period following its ingestion. Thirty minutes after administration of 0.65 g. of acetylsalicylic acid 27 per cent of the total salicylate of the plasma was acetylsalicylate; at 120 minutes, none could be found. Seventy minutes after 2.60 g., 13 per cent of the total salicylate was present as acetylsalicylate; at 160 minutes, none could be found. The investigators advanced the theory that the analgesic action of acetylsalicylate is exercised mainly by the unhydrolyzed acetylated fraction in the plasma.

Some Factors Influencing Concentration of Salicylate in Blood and Plasma

It has long been observed that sodium salicylate, as well as other salicylates, is better tolerated in large doses when taken with sodium bicarbonate. This beneficial effect of bicarbonate was attributed, for the most part, to a diminishing of irritation of the gastric mucosa and to counteraction of the acidosis formerly believed to be present after large doses of salicylate. More recently interest has turned to another influence shown particularly with bicarbonate and to some extent also with other substances and procedures: the effects exercised on absorption and elimination and thus on the concentration of salicylates in the blood and plasma.

The initial work in this direction was that of Blume and Nohara [1933] who reported that, in rabbits, injections of calcium gluconate prior to the administration of salicylates evoked an increase in the rate at which the concentration of salicylate developed in the blood.

Herrera-Ramos [1937 (1569)] concluded from experiments on dogs that sodium bicarbonate administered with salicylate doubles or even triples the concentration of salicylate in the blood.

Myung [1938], using rabbits, showed that cutting the vagi or giving atropine or adrenalin lowered the level to which salicylate rose in the blood and increased the urinary secretion of salicylate. Cutting the splanchnic nerve or giving ergotine or choline had the reverse effect. When rabbits were given chloral hydrate, urethane, morphine or heroin, and later a subcutaneous injection of salicylate, they developed a higher concentration of salicylate in the blood

received at 6-hour intervals five 2-g. doses of sodium salicylate, ammonium salicylate or acetylsalicylate. Concentrations of salicylate in the plasma were determined at 6, 12, 24, 36 and 48 hours. The findings are summarized in Figure 9 and it may be seen that there were no appreciable differences among the concentrations obtained with the various drugs. These investigators (3274) reported that they were unable to find any unchanged acetylsalicylate in the plasma following administration of this drug to men and dogs.

Lolli and Smith [1946] administered 0.6 and 1.6 g. of acetylsalicylic acid to two normal fasting subjects. Blood samples were drawn and analyzed for salicylate at $\frac{1}{2}$, 1, 2 and 4 hours. With 0.6 g. the blood concentrations at these times were 0.80, 1.80, 3.80 and 2.65 mg. per 100 cc.; with 1.6 g. they were 1.67, 3.67, 5.53 and 7.33 mg. per 100 cc.

In studying the fate of acetylsalicylic acid, Lester, Lolli and Greenberg [1946] determined the concentration of salicylate in the plasma of normal human subjects after administration of small single doses of acetylsalicylic acid. Two typical curves of concentrations are shown in Figure 4; they were obtained after adminis-

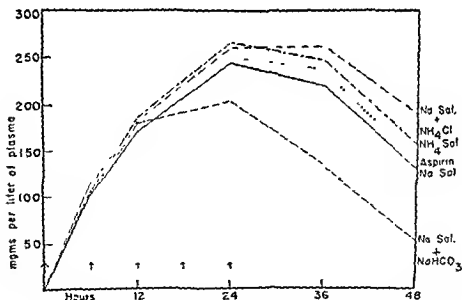


FIGURE 9.—Concentrations of salicylate in plasma after administration of five doses of various salicylates at 6-hour intervals, indicated by arrows. Reproduced from Smith, Gleason, Stoll and Orgorzałek (3274).

and a smaller urinary excretion of salicylate than did normal animals. The degree of difference depended on the extent of narcosis and not on the drug used. In rabbits given caffeine-sodium benzoate, picrotoxin or strychnine, the concentration of salicylate in the blood was considerably lower than in normal animals and the urinary excretion was greater.

Smull, Wégria and Leland [1944] observed the effect of sodium bicarbonate on the concentration of salicylate in the serum of four rheumatic patients and four healthy subjects receiving repeated daily administrations of sodium salicylate. From their data, shown in Figure 10, it may be seen that sodium bicarbonate decreased the concentration of salicylate in the serum by 44 per cent in normal subjects and by 53 per cent in rheumatic patients.

Coombs [1945] observed the effect of sodium bicarbonate on the concentration of salicylate in the serum of a patient receiving oral salicylate therapy for 3 weeks. The concentration had been maintained at a level of about 55 to 65 mg. of salicylate per 100 cc. for 2 weeks. When 6 g. of bicarbonate per day were added, the concentration dropped after 5 days to 45 mg. per 100 cc.

Smith [1945 (3272)] determined the concentration of salicylate in the plasma of 30 nonfebrile rheumatic patients who received five 2-g. doses of sodium salicylate at 6-hour intervals. Some also received equal doses of sodium bicarbonate and others ammonium chloride with the salicylate. His data (Figure 11) indicate that with sodium bicarbonate there is a slightly lower concentration of salicylate in the plasma; with ammonium chloride there is a slightly higher concentration. Smith postulated that these results are due, in part, to the effect of bicarbonate and ammonium chloride on the urinary excretion of salicylates.

Keith and Ross [1945] also found that sodium bicarbonate diminishes the concentration of salicylate in plasma of human subjects. Five to 10 g. of sodium salicylate or acetylsalicylic acid produced concentrations the same as or higher than did 10.0 to 13.3 g. with an equivalent amount of bicarbonate. Sodium salicylate produced concentrations of salicylate in the plasma similar to those produced by acetylsalicylic acid.

Smith and his associates [1946 (3274)] demonstrated that in rheumatic and nonrheumatic subjects receiving sodium salicylate or acetylsalicylic acid therapy, ammonium chloride caused a slight elevation of the concentration of salicylate in the plasma, while

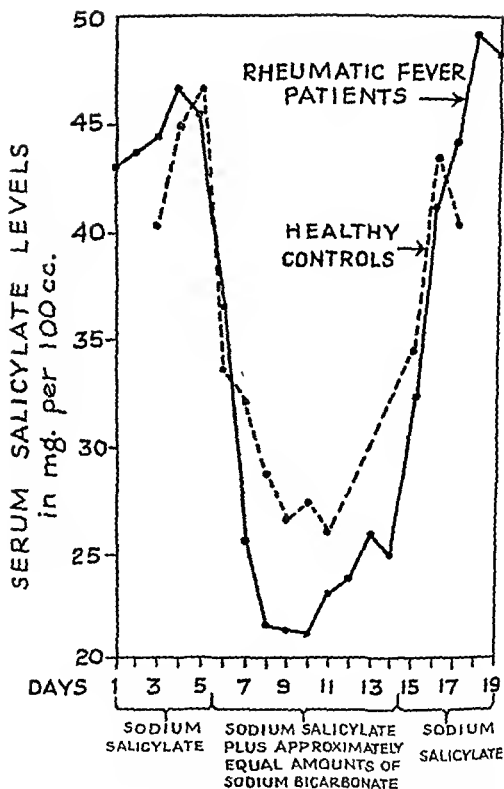


FIGURE 10.—Concentrations of salicylate in serum of four rheumatic patients and four healthy subjects after sodium salicylate with and without sodium bicarbonate. Based on data of Smulj, Wégria and Leland (3277).

and a smaller urinary excretion of salicylate than did normal animals. The degree of difference depended on the extent of narcosis and not on the drug used. In rabbits given caffeine-sodium benzoate, picrotoxin or strychnine, the concentration of salicylate in the blood was considerably lower than in normal animals and the urinary excretion was greater.

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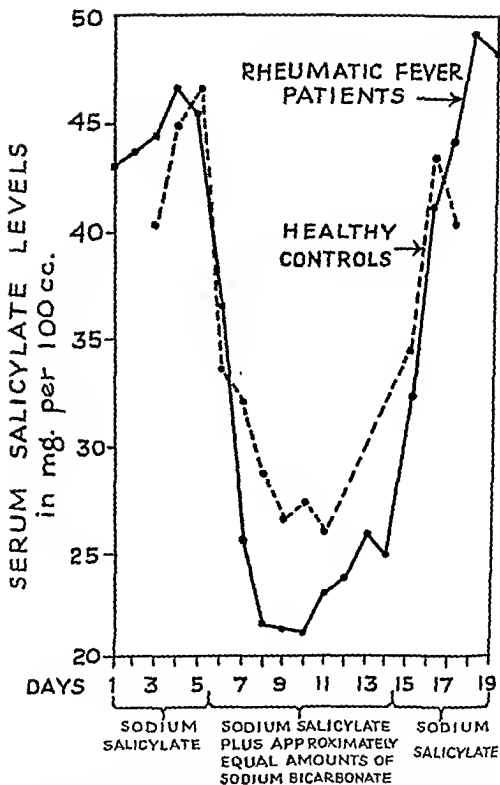


FIGURE 10.—Concentrations of salicylate in serum of four rheumatic patients and four healthy subjects after sodium salicylate with and without sodium bicarbonate. Based on data of Smull, Wégria and Leland (3277).

Lester, Lolli and Greenberg [1946] found that in normal subjects 1 and 2 g. of sodium bicarbonate given with small doses of acetylsalicylic acid (0.65 and 1.30 g.) hastened the rise of the concentration of salicylate in the plasma (Figure 3). The maxi-

TABLE 7.—*Effect of an Effervescent Mixture, Sodium Citrate, Sodium Tartrate, and Carbonated Water, on Concentrations of Salicylate in Blood following Ingestion of Acetylsalicylic Acid**

Subject 1	Dose of Acetyl-salicylic Acid (g.)	CONCENTRATION OF SALICYLIC ACID (MG./100 CC.)			
		½ hr.	1 hr.	2 hr.	4 hr.
Drug alone	1.6	1.67	3.67	5.53	7.33
Drug and effervescent mixture	1.6	...	8.93	10.20	10.30
Drug and sodium citrate (4 g.)	1.6	3.00	4.06	6.00	9.20
Drug and sodium tartrate (4 g.)	1.6	4.47	5.86	10.01	8.40
Drug and carbonated water	1.6	2.53	3.86	8.34	9.85
Subject 2					
Drug alone	0.6	0.80	1.80	3.80	2.65
Drug and effervescent mixture	0.6	4.33	4.10	3.53	2.20
Drug and sodium citrate (4 g.)	0.6	4.25	4.06	3.87	2.60
Drug and sodium tartrate (4 g.)	0.6	1.40	3.00	3.35	2.74
Drug and carbonated water	0.6	1.80	3.50	3.80	2.33

*Data of Lolli and Smith (2191).

mum concentration was the same as that obtained when no bicarbonate was given, but was reached much sooner. The effect is attributed to an increased rate of absorption.

Caravati and Cosgrove [1946] gave sodium bicarbonate to rheumatic patients undergoing continuous salicylate medication. The concentration of salicylate in the plasma dropped 36 per cent after oral and 41 per cent after intravenous administration and the urinary secretion of salicylate increased about 50 per cent. In one patient with a concentration of 26 to 28 mg. of salicylate per 100 cc. of plasma, 4 g. of ammonium chloride daily for 2 days increased the concentration to between 35 and 40 mg. per 100 cc. When the ammonium chloride was discontinued, the concentration dropped back to 26 mg. per 100 cc.

Concentration of Salicylate in Spinal Fluid

Olmer and Tian [1909] gave three subjects 2 g. of lithium salicylate daily for 8 to 10 days. The lithium content of the spinal fluid was determined spectroscopically. From the appreciable amounts of lithium found in this fluid the investigators concluded that lithium salicylate penetrates into the spinal fluid. Since the lithium ion may

sodium bicarbonate caused a marked depression of the concentration of salicylate in the plasma. Their data are summarized in Figure 9. The effect of the bicarbonate is attributed to an increased excretion of salicylate, the renal clearances of free salicylate increasing rapidly when the pH of the urine was above 7.

In two normal fasting subjects given 0.6 and 1.6 g. of acetylsalicylic acid, Lolli and Smith [1946] observed the effects on concentrations of salicylate in the blood of (a) an effervescent mixture of tartaric acid (3 g.) and sodium bicarbonate (4 g.); (b) sodium citrate (4 g.); (c) sodium tartrate (4 g.); and (d) carbonated water (150 cc.). The blood of each subject was analyzed for salicylate at $\frac{1}{2}$, 1, 2 and 4 hours. The findings are shown in Table 7. All of the adjuvant substances administered caused a more rapid rise and a higher maximum concentration of salicylate in the blood. These effects are attributed to a hastening of gastric emptying, and hence a more rapid absorption.

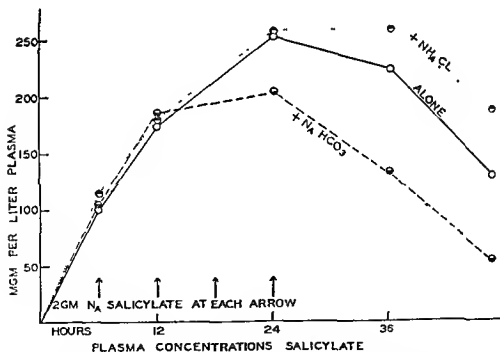


FIGURE 11.—Concentrations of salicylate in plasma after administration of five 2-g. doses of sodium salicylate alone and with equal amounts of sodium bicarbonate and ammonium chloride. Reproduced from Smith (3272).

salicylic acid was found in the plasma, but 1.0 mg. per 100 cc. was present in the spinal fluid at 1 hour and none at 5¼ hours. The fact that acetylsalicylic acid appears in the cisternal fluid when none is present in the blood indicated to these investigators that it is protected in the spinal fluid from the hydrolysis which occurs rapidly in the blood.

Concentration of Salicylate in the Brain

Hanzlik [1927] administered sodium salicylate to dogs and cats in doses of 180 to 400 mg. per kg. and found that the concentration of salicylate in the brain was from one-seventh to one-

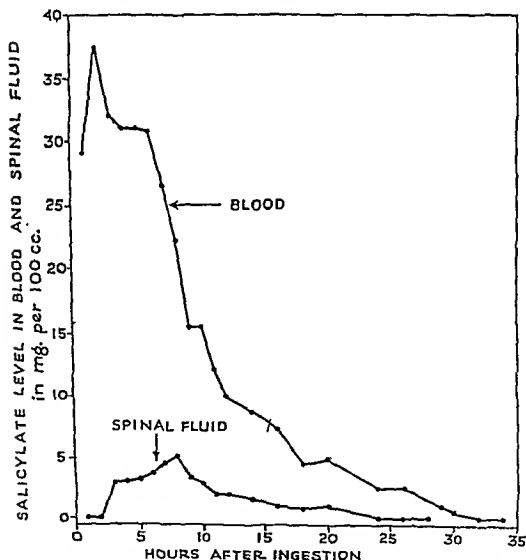


FIGURE 12.—Concentrations of salicylate in blood and spinal fluid after administration of sodium salicylate. Based on Bérnard and Daniel (277).

well penetrate the spinal fluid without the salicylate ion doing so, this conclusion cannot be accepted from the evidence presented.

Marfan and Lagane [1911] detected no salicylate in the spinal fluid of 1 adult and 11 children receiving 1 to 4 g. of sodium salicylate daily. Rotky [1912] likewise found no salicylate in the spinal fluid of 2 patients, 1 of whom had received 2 g. of sodium salicylate within 12 hours and the other, 20 g. of theobromine sodium salicylate in the course of 5 days.

Nobécourt, Darré and Bidot [1912] examined for salicylate the spinal fluid of 14 children who had received from 4 to 22 g. of salicylate over a period of 2 to 23 days. In 9 instances salicylate was present in the spinal fluid; in 6 instances it was absent. They could show no relationship between the amount of salicylate administered and the concentrations developed in the spinal fluid.

Loberg [1928] compared the concentration of salicylate found in the spinal fluid and blood serum of 24 subjects who had received 20 mg. of sodium salicylate per kg. every 5 hours for 45 hours. Blood was drawn and lumbar puncture performed 1 hour after the last dose. Concentrations of salicylate in the spinal fluid varied from none to 7.8 mg. per 100 cc. (average 2.6); in serum, from 13.9 to 40.5 mg. per 100 cc. (average 30.9).

Sicard [1928] stated that after oral administration for clinical purposes, salicylate practically never appears in the spinal fluid. Given in large doses, however, sodium salicylate may penetrate the hemoencephalic barrier.

Bérnard and Daniel [1933] compared the content of salicylate in blood and spinal fluid after administering sodium salicylate. The amounts of the drug, the mode of administration and the animal used were not stated. The findings reported are shown in Figure 12.

Lester, Lolli and Greenberg [1946] gave a dog intravenous injections of sodium salicylate at the rate of 20 mg. per kg. per hour for 7 hours. At 5 and 8 hours the concentration of salicylate in the cisternal fluid was about one-third that in the plasma. Another dog was given 200 mg. of acetylsalicylic acid per kg. in a single dose intravenously and plasma and cisternal fluid were examined for salicylate 1 and $5\frac{1}{4}$ hours later. Between these two times the concentration of salicylate in the plasma decreased from 34.8 to 22.3 mg. per 100 cc. but that of the cisternal fluid increased from 4.0 to 6.6 mg. per 100 cc., indicating that the concentration in the spinal fluid lags behind that in blood and plasma. No acetyl-

rabbits. Concentrations of salicylate were found in decreasing order in serum, joints, muscles and bones.

Falk and Todesco [1910], after administering sodium salicylate, found salicylate in the sputum of patients with pneumonia and tuberculosis but none in that of patients having acute, chronic, congestive or suppurative bronchitis. Armstrong and Goodman [1911], however, found no salicylate in the sputum after it had been administered to 19 patients having various lung diseases including pneumonia and tuberculosis.

After administering 1 g. of sodium salicylate to rabbits Jurgens [1920] found concentrations of salicylate in decreasing order in kidneys, joints, lungs and muscles.

Gifford [1922] reported that the content of salicylate in the fluids of the inflamed eyes of cats and rabbits which had received salicylate was no greater than in normal eyes. The concentration was lower in the blood than in the aqueous humor.

Smith and his associates [1946 (3274)] studied the distribution of salicylate in various tissues of rats given sodium salicylate and found that the concentrations in the water of the liver, kidneys, lungs and whole blood were approximately the same as that in the serum while the concentrations in the water of the muscle and brain were approximately half as high.

Lester, Lolli and Greenberg [1946] injected saline solution into the peritoneal cavity of rats which had been given 200 mg. of sodium salicylate per kg. intravenously. After 2 hours they found the concentrations of nonprotein-bound salicylate in blood and peritoneal saline to be equal. This was taken as evidence in support of their belief that, at equilibrium, the concentration of nonprotein-bound salicylate is the same in all body water to which salicylate has access.

There are five deaths on record in which quantitative determinations of salicylate were made in organs and body fluids. Three are cases of suicide by acetylsalicylic acid (Balázs [1932 (134)], Halstrøm and Møller [1939] and Orzechowski [1936]); one is a case of accidental poisoning from the ingestion of methyl salicylate by a 10-month-old infant (Arnold and Jacobsen [1927]); and one is the case of a patient with rheumatic fever who received large daily doses of sodium salicylate up to the time of death (Quinke [1882]). The concentrations found are shown in Table 8.

half that in the blood and the spleen, and one-sixth to one-third that in the muscles and intestine. After administration of methyl salicylate and acetylsalicylic acid, essentially the same differences in distribution were found. In view of the difficulties reported by Hanzlik and Wetzel [1920 (1480)] in attempts to determine the content of salicylate in various tissues, the quantitative significance of these data may be open to some doubt.

Concentration of Salicylate in Joints

Filippi and Nesti [1902] reported that 2 hours after administration of 2 g. of acetylsalicylic acid to five rheumatic patients the synovial fluid gave a stronger salicylate reaction than the urine. In the ascitic fluid only a trace of salicylate was found.

Scott, Thoburn and Hanzlik [1917] determined the concentrations of salicylate in the blood and synovial fluid of five rheumatic patients receiving salicylate. At concentrations of salicylate in the blood of 14, 16, 20, 23 and 30 mg. per 100 cc. the corresponding values in the synovial fluid were 11, 11, 18, 25 and 23 mg. per 100 cc. The average of the concentrations in the blood was 20 mg. per 100 cc.; that of synovial fluid, 18 mg. per 100 cc. The investigators concluded that in rheumatic individuals the concentration of salicylate is approximately the same in blood and joint fluids.

Fröhlich and Singer [1923] determined the salicylate in the synovial fluid of the knee joints of nine rabbits given 2 to 5 g. of sodium salicylate. In each animal inflammation of one of the joints was produced by injection of croton oil or bacteria. No constant difference was found between the concentration of salicylate in the inflamed joint and that in the normal one.

Concentration of Salicylate in Other Organs and Body Fluids

Benicke [1876] gave 1.5 to 2.0 g. of salicylic acid to women in labor 10 minutes to 26 hours before childbirth. The babies were catheterized before the first feeding. In two instances, where the salicylate was given 10 and 15 minutes before birth, none was found in the urine; in all other instances the urine contained salicylate.

Bondi and Jacoby [1906] administered 0.75 g. of salicylic acid, sodium salicylate, acetylsalicylic acid or amidosalicylic acid to

BINDING BY PROTEINS

The first suggestion that salicylate in the body is bound to protein appeared in 1875 when Feser and Friedberger (1099), unable to extract salicylates from blood by ether, hypothesized therefore that salicylate circulates in the body in the form of an albuminate. This hypothesis was disputed by Fleischer [1876], who pointed out that the salts of salicylic acid are not soluble in ether and for this reason are not extractable from blood.

In 1908 Jacoby (1745) stated that salicylate could be bound to serum constituents, and he concluded from experiments on rabbits that it was, in fact, bound in some manner to the serum proteins or polypeptides. When serum obtained from rabbits receiving sodium salicylate was acidified with sulfuric or acetic acid, salicylate could be extracted with ether. The protein precipitate obtained from the serum by heating contained only traces of salicylate. The precipitate obtained by half saturation with ammonium sulfate likewise contained little or no salicylate, while that obtained by full saturation with ammonium sulfate contained considerable amounts. Although Jacoby's conclusion on the binding of salicylate with protein has been borne out by later investigation, its justification from his work is difficult to understand. It appears more likely that his results were simply an expression of differences in the solubility of the salicylate in serum-salt mixtures of different pH. He further found that the addition of sodium salicylate to normal rabbit serum resulted in no precipitation of the salicylate on full saturation with ammonium sulfate. He concluded from this that no binding occurred if the salicylate was added *in vitro* to serum. No investigator has since been able to reproduce this phenomenon.

In 1923 Chabanier, Lebert and Lobo-Onell (620, 621) gave the first logical proof of the binding of salicylate in serum. Their experiments were based on the fact that salicylate bound to protein would not pass through a semipermeable membrane, whereas unbound salicylate would. Serum containing sodium salicylate lost practically none of the salicylate to isotonic saline on prolonged dialysis. Serum dialyzed against isotonic saline containing salicylate rapidly gained salicylate, which virtually disappeared from the saline. From these observations, and from a study in human subjects of the rate of excretion of salicylate by the kidneys, these investi-

It is apparent from the literature dealing with the concentrations of salicylate in body fluids and tissues that the relationship between the amount administered and the concentration found is not a predictable one. This is due to variations in the distribution

TABLE 8.—*Concentration of Salicylate in Organs and Body Fluids in Five Deaths after Large Doses of Salicylate*

	Balázs (134)	Halström and Møller (1445)	Orzechowski (2636)	Arnold and Jacobsen (91)	Quincke (2836)
	<i>Acetylsalicylic Acid</i>	<i>Acetylsalicylic Acid</i>	<i>Acetylsalicylic Acid</i>	<i>Methyl Salicylate</i>	<i>Sodium Salicylate</i>
Sex	Female	Male	Male	Male	Female
Age	52 yr.	43 yr.	31 yr.	10 mo.	17 yr.
Dose taken	35 g.		94-100 g.	10 cc.	12 g./day
Time from ingestion to death	17-18 hr.			16½ hr.	
	CONCENTRATION OF SALICYLATE (MO. PER 100 CC. OR G.)				
Brain	1.6	20.0	0.04		none
Liver	5.5	46.5	0.80	30.0	traces
Kidneys	8.0	82.4		50.0	strong
Blood	15.0	0.6	2.20		10.0
Pericardial exudate					45.0
Spleen		36.1			
Bile			2.50	10.0	traces
Muscle		29.4		20.0	
Content of small intestine		34.4	1.30		
Urine			88.20	110.0	198.0
Gastric juice			162.80		
Liver blood			1.10		
Joints			2.20		

of salicylate among the different fluids and tissues and to the effect of the pH of the urine on the rate of excretion of salicylate by the kidneys, especially as influenced by the administration of acids and alkalis. Although it has been suggested that the nonprotein-bound salicylate is distributed equally throughout all of the body water to which it has access, this access is slow to some fluids, such as the spinal fluid and fluids of the eye. The binding of appreciable amounts of salicylate to certain proteins in the body, a factor which will be considered later, further subjects the distribution of salicylate to variations depending upon the distribution in the body of the salicylate-binding proteins. Thus the concentration is disproportionately high in the plasma, compared to other body fluids, because of the high proportion of salicylate-binding protein in the plasma.

Lester, Lolli and Greenberg [1946] studied the ability of human plasma to bind salicylate both *in vivo* and *in vitro*. Both dialysis and ultrafiltration were used. They found, as had Smith and his associates, that the proportion of bound salicylate in plasma decreases with increasing concentrations of total salicylate. At a level of 4 mg. per 100 cc., 90 per cent was bound; at 16 mg. per 100 cc., 70 per cent; at 70 mg. per 100 cc., 54 per cent. In rheumatic fever patients receiving salicylate therapy a much lower proportion of salicylate was bound in plasma than in normal individuals having the same concentration of salicylate in the plasma. In one instance only 6 per cent was bound at a total concentration of salicylate in the plasma of 37 mg. per 100 cc. The binding of salicylate in plasma *in vitro* was found to diminish with decreasing concentrations of protein. Variations of temperature from 6° C. to 37° C. were found to be without appreciable effect on the extent of binding. Finally, it was found that unconjugated salicylate is bound much more readily than is acetylsalicylate.

The high concentration of salicylate occurring in plasma, as compared with that in the red cells, has been known for some time.

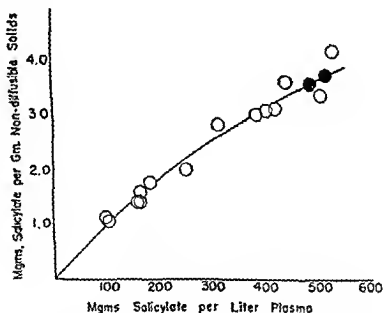


FIGURE 14.—Relationship between concentration of salicylate in plasma and amount of salicylate bound to plasma proteins. Black circles represent *in vitro* experiments. Reproduced from Smith, Gleason, Stoll and Orgorzalek (3274).

THE SALICYLATES

gators concluded that both *in vitro* and *in vivo* only a small part of the total salicylate held by the serum is unbound.

Storm van Leeuwen and Drzimal [1924], from experiments with *in vitro* dialysis, reported that the serum of asthmatic patients had a lesser capacity to bind salicylate than that of normal individuals.

Protein-bound salicylate does not pass through a cellophane ultrafilter, whereas unbound salicylate does. By means of ultrafiltration Smith and his associates [1946] studied the extent of salicylate binding in the plasma of patients receiving salicylate. Figure 13 shows the relationship found between the total salicylate in the plasma and the unbound salicylate in the plasma and the amount bound to plasma proteins. At concentrations of salicylate in the plasma of 200 mg. per liter, less than 50 mg. were unbound, but at 500 mg. per liter almost half was unbound. There was no evidence that at concentrations over 500 mg. per liter the ability of the plasma proteins to bind salicylate was exhausted. These investigators demonstrated that variations of pH between 7.41 and 8.12 were without effect upon the degree of binding.

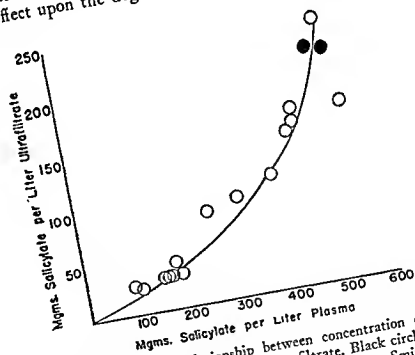


FIGURE 13.—Relationship between concentration of salicylate in plasma and plasma ultrafiltrate. Black circles represent *in vitro* experiments. Reproduced from Smith, Gleason, Stoll and Orgorzalek (3274).

of salicylate found in plasma, which has a high content of salicylate-binding protein.

It is also possible that the binding of salicylate with protein is a factor in some of the therapeutic actions of salicylate; this feature, as well as the effects of salicylate binding on the urinary excretion of the drug, will be discussed later.

METABOLISM

The greater part of salicylate absorbed into the body through any channel undergoes a chemical alteration in the process of metabolism: the esters of salicylic acid are hydrolyzed; salicylic acid is conjugated; and the salicylate radical is oxidized. As will be shown in the following section dealing with the elimination of salicylate, three-fourths of administered salicylate is eliminated in the form of compounds containing the still intact salicyl group.

That partial hydrolysis of salicylate esters may take place in the gastrointestinal tract before absorption is evident from the literature reviewed in a previous section dealing with absorption; after absorption, completion of hydrolysis is rapid. Little experimental evidence has been reported concerning the presence of esters of salicylic acid in the body after their administration. Smith and his associates [1946] were unable to find any acetylsalicylate in the plasma after its administration to men and dogs. Lester, Lolli and Greenberg [1946] found acetylsalicylate present in the plasma of human subjects for a short period following its ingestion. There are no data in the literature concerning the presence or absence of other salicylate esters in the blood following their administration.

That a portion of some administered esters of salicylate may pass through the body unaltered is suggested by the reported urinary excretion of small amounts of these esters. The presence of acetylsalicylic acid in the urine after oral administration was reported by Pitini [1920], Devrient [1921], Hanzlik and Prescho [1923, 1925 (1471)] and Quick [1933]. Bondi and Katz [1911] and Chistoni [1924] were unable to confirm this. Following their administration, phenyl salicylate, ethyl salicylate and methyl salicylate were reported in the urine by Baas [1890], methylene citrylsalicylic acid by Dreser [1907], salicylsalicylic acid by Hanzlik and Prescho [1925 (1471)] and methyl salicylate by Hanzlik and Prescho [1925 (1472)] and Hanzlik and Wetzell [1920 (1481)]. In most of these observations, however, the presence of the un-

Friderichsen [1917] and Herrera-Ramos [1938 (1571)] observed this difference but offered no explanation for it. Smith and his associates [1946] also pointed out that the amounts of salicylate in the red cells were much lower than in the plasma. They added the observation, however, that the amounts found in the red cells are of the same order of magnitude as might be expected if the cell membrane were freely permeable to the salicylate contained in the plasma ultrafiltrate. Lester, Lolli and Greenberg [1946] studied the distribution of salicylate between red cells and plasma in human blood and showed that there is no binding of salicylate by the protein of the red cell, that the concentration of salicylate in the water of the cells is identical with that of the unbound salicylate and that the peculiar distribution between the red cells and plasma is due entirely to the binding of the salicylate by plasma proteins.

Undoubtedly, important features of the distribution and excretion of salicylate in the body are attributable to protein binding. The exceptionally high concentration of salicylate found in plasma, in proportion to the amount of drug administered, has never been commented on by the numerous investigators. Most of them have offered no explanation for the widely uneven distribution of salicylate in the various fluids, tissues and organs of the body except in regard to the spinal fluid, in which case the hematoencephalic barrier was presumed to be penetrated slowly or not at all by salicylate. In a study as recent as that of Smith and his associates [1946] the only explanation suggested for the concentration of salicylate found in some tissues was that it was in equilibrium with that in the serum. In respect to other tissues, where much lower amounts of salicylate were found, no explanation was suggested. Although these investigators were aware of and discussed the binding of salicylate in their work, no reference to this phenomenon as a possible explanation for the peculiar distribution of salicylate in the body was made.

Lester, Lolli and Greenberg [1946], however, concluded from their observations that only unbound salicylate is distributed equally throughout the extracellular and perhaps the intracellular water of the body, and that the total salicylate content of any body fluid depends upon its content of salicylate-binding protein. Thus a plausible explanation was offered for the unequal distribution of salicylate in body tissues and fluids and for the high concentration

salicylic acid in the urine of patients receiving sodium salicylate and concluded that conditions in patients with rheumatic fever facilitated the liberation of salicylic acid.

After a lapse of 40 years this question of salicylic acid and its sodium salt was again raised by Scott, Thoburn and Hanzlik [1917], who found no salicylic acid in the exudates from joints of rheumatic fever patients. Four years later Hanzlik [1921] determined the acidity necessary for the liberation of salicylic acid from a solution of sodium salicylate and found that at pH 8.4 to 7.0 no salicylic acid was extractable by ether. At pH 6.7 a small amount was extractable, and this amount increased with rises in acidity. Boots and Cullen [1922] pointed out that no free salicylic acid can exist in the joint fluids of rheumatic fever patients since the exudates of 16 such patients studied were all slightly alkaline. This controversy did not in reality concern the metabolism of salicylate but was only a question of the acidity of the medium containing the salicylate ion.

Directly pertinent to the metabolism of free salicylate have been the studies dealing with the oxidation and conjugation of salicylate in the body. The difference between the amount of salicylate administered and that eliminated has been presumed to represent the amount oxidized in the body. That metabolic products resulting from the oxidation of salicylate were present in the urine was first suggested by Baldoni [1908]. He isolated these products from the urine of dogs given sodium salicylate and referred to them as uraminsalicylic acid and ursalicylic acid. Neuberg [1911], using Baldoni's method of extraction, isolated a compound from the urine which gave no reaction with orcin, phloroglucin or naphthoresorcin, was reducing after being heated, and gave a blue color with ferric chloride. He concluded that this substance was 1,2,5-dioxybenzoic acid or gentisic acid. Angelico [1921] confirmed the observations of Baldoni. The crystallized metabolite he obtained had a melting point of 197° to 198° C., yielded the empirical formula of gentisic acid, and on heating with sulfuric acid was transformed to hydroquinone.

In 1942 Kapp and Coburn (1825) confirmed the occurrence of gentisic acid and a small amount of some other product of salicylate oxidation which they referred to as Baldoni's "Uraminsalicylsäure." The amounts of these metabolites which they found, however, accounted for only 4 to 8 per cent of the ingested salicylate.

altered salicylate esters in the urine was merely inferred from the difference between the amount of salicylic acid analyzed before and after hydrolysis of the urine. As suggested by Smith and his associates [1946], the more recent work of Kapp and Coburn [1942] raises considerable doubt as to the validity of this inference since the differences observed after hydrolysis may have been due to the presence of endogenous conjugates of salicylate rather than the administered ester.

Whether or not a small amount of salicylate ester appears in the urine after its administration, it is certain that the major portion, if not all, is hydrolyzed in the body with the liberation of free salicylate.

Free salicylate given as such or resulting from the hydrolysis of salicylate esters in the body is in small part eliminated unchanged. Kapp and Coburn [1942] found that in normal human subjects about 20 per cent of excreted salicylate is free salicylate. Smith and his associates [1946] found 6 to 26 per cent of eliminated salicylate as the free compound. Lester, Lolli and Greenberg [1946] reported that free salicylate constituted 20 to 25 per cent of the total salicylate eliminated.

The major portion of free salicylate introduced into the body or liberated in it by hydrolysis undergoes metabolic changes. The earliest observations intended to deal with the intermediary metabolic products of free salicylate were concerned with the question of whether the salicylate is present in the body as the acid or as the sodium salt. These observations received their impetus from the early and now discarded concept that salicylic acid, but not sodium salicylate, has antiseptic power and that free salicylic acid must be liberated in the blood and tissues to produce an antiseptic and therefore therapeutic action in rheumatic fever. Thus Salkowski [1875] examined the antiseptic power of salicylic acid *in vitro* and concluded that this substance is useless internally since, due to the alkalinity of the blood, it is turned into the sodium salt. Von Meyer and Kolbe [1875 (2417)] added salicylic acid to dog serum and were able to extract only a portion of it with ether, but acidification of the serum resulted in an increase in the amount extractable. On this basis they suggested the dubious procedure of giving acid to patients before salicylate medication. Although Fleischer [1876] showed, in experiments with men and dogs, that salicylic acid becomes a salt in the blood, Binz [1876 (304)] reported finding

the excretion of glucuronic acid was doubled in one subject and tripled in the other. Galimard [1944] also found that the total glucuronic acid excreted in the urine increases with the amount of salicylate excreted. The assumption made from these observations was that the increase in elimination of glucuronic acid is due to the excretion of salicyl-glucuronides.

Quick [1932 (2831)] studied the urinary excretion of salicyl-glucuronic acid in dogs after feeding salicylic acid and found that in the urine o-hydroxybenzoic acid (salicylic acid), like p-hydroxybenzoic acid, is combined with two molecules of glucuronic acid. Kapp and Coburn [1942], in a thorough study of the urinary metabolites of sodium salicylate, found that in normal human subjects about 25 per cent of the salicylate excreted appears as a mono- or di-glucuronide. From the data of Smith and his associates [1946], 16 to 19 per cent of the salicylate excreted may be calculated to be sulfuric or glucuronic acid conjugates. Lester, Lolli and Greenberg [1946] found approximately 20 per cent of the eliminated salicylate to be these conjugates.

Considerable data have been reported in the literature concerning the presence in the urine of a third conjugate of salicylic acid, salicyluric acid. This is formed by the combination of the amino acid, glycine, on the carboxyl group of the salicylic acid. The occurrence of this compound as a final metabolic product of salicylic acid was first reported by Bertagnini [1856]. His findings received early confirmation by von Nencki [1870], Gnehm [1875], Pye-Smith [1878], Baldoni [1905, 1909, 1915 (143), 1923 (144, 145)], and Neuberg [1911]. Mosso [1889] reported that in man 80 per cent of the excreted salicylate appears as salicyluric acid, and in dogs 20 per cent. Stockman [1906 (3351)] found that the excretion of salicyluric acid varied from small traces to half the amount of salicylate administered. Drzimal [1924] reported that 13 per cent of the total salicylate excreted is salicyluric acid; Chistoni [1924], 73 and 80 per cent; and Holmes [1925], approximately 60 per cent.

Wiley [1906], in men, and Hanzlik [1917] in men, dogs and cats, were unable to find salicyluric acid in the urine after administration of salicylate. Quick [1932 (2831)] likewise concluded that in experiments on human subjects no salicyluric acid is excreted after administration of salicyluric acid. However, a year later this investigator (2832) reported data showing that one-third to one-

Salicylic acid is capable of conjugation in the body with sulfuric and glucuronic acids on the hydroxyl group and with the amino acid, glycine, on the carboxyl group. No experimental data have been reported to demonstrate the presence of any of these conjugates in the blood or plasma. Smith and his associates [1946] found only free salicylate in the plasma after administration of acetylsalicylic acid. Besides a small amount of acetylsalicylate, occurring in the plasma for a short time after its administration, Lester, Lolli and Greenberg [1946] likewise found only free salicylate; after administration of sodium salicylate they found free salicylate but no ester in the plasma.

The occurrence in the urine, however, of abundant amounts of conjugates of salicylate has often been reported. The possible presence in the urine of the sulfuric acid conjugate of salicylate has been suggested in the literature. Baumann and Herter [1877] found an unusually large amount of ethereal sulfate in the urine of a dog given sodium salicylate. Neuberg [1911] showed that the ratio of ethereal sulfate to total sulfate increased markedly in the urine of a dog after administration of salicylic acid.

Reports of the excretion of the glucuronic acid conjugate of salicylate have been far more numerous. Byasson [1877] observed that the urine of patients who had taken salicylates reduced Fehling's solution. From similar observations and from the fact that the urine gave positive orcin and phloroglucin tests after the administration of salicylate, Neuberg [1911] concluded that salicylglucuronic acid was excreted. Baldoni [1905] extracted a compound from the urine of dogs given sodium salicylate which, from chemical analysis, melting point and chemical reactions, he believed at the time to be salicylglucuronic acid. In a later publication [1908] he concluded that this material was actually a mixture of two other compounds: uraminsalicylic acid and ursalicylic acid. He was able to demonstrate the probable presence of salicylglucuronic acid in the urine of dogs, but was unable to isolate it, using his own technique.

Tollens [1909] and Tollens and Stern [1910] found an increase in the amount of glucuronic acid in the urine of men after administration of salicylic acid. Maugham, Evelyn and Browne [1938] determined the urinary elimination of glucuronic acid in two normal subjects for 3 to 6 days before and 2 days after administration of 3 g. of acetylsalicylic acid. They found that following the salicylate

found considerably larger amounts in the urine of man. They compared the urinary excretion of salicylate after administration of sodium salicylate, methyl salicylate, acetylsalicylic acid and salicylsalicylic acid in doses of 0.5 to 1.0 g. After sodium salicylate 80 per cent of the salicylate was excreted in the urine; after the salicylate esters only 60 per cent was excreted. Hanzlik and Preshe [1923] made similar determinations for doses of 4.0 to 14.8 g. of acetylsalicylic acid and recovered from 27.0 to 101.4 per cent of the salicylate administered. Chistoni [1924] gave 1 g. of acetylsalicylic acid to each of two subjects and recovered virtually all of the salicylate in the urine.

The extreme variability of the values for the amount of salicylate excreted in the urine, as reported up to 1924 by the different investigators as well as by the same groups of investigators, raises some doubt as to the validity of the findings. On one hand, recoveries of 100 per cent were reported, indicating that no oxidation of salicylate occurs in the body; at the other extreme, recoveries as low as 23 per cent were reported, suggesting that the major portion of the salicylate is oxidized. Neither of these conclusions is compatible with the data, discussed previously, concerning the amount of salicylate oxidized in the body.

There is greater uniformity in the more recent reports of the amount of salicylate excreted in the urine. Johnson and Hanzlik [1929] found approximately 80 per cent of the ingested salicylate eliminated in the urine by subjects given 4 g. of ammonium salicylate. Blume and Breunig [1931] recovered 54 to 83 per cent in the urine of rabbits given 0.25 g. of sodium salicylate. Kapp and Coburn [1942] recovered from 70 to 85 per cent in the urine of children given sodium salicylate. In the urine of patients given 2 to 8 g. of salicylate for 1 to 14 days Bauer [1944] recovered 81 per cent. In 35 experiments Lester, Lolli and Greenberg [1946] recovered an average of 68 per cent in the urine of subjects given 0.33 to 1.95 g. of acetylsalicylic acid. These more recent data are in closer correspondence with the amounts of salicylate reported to be oxidized in the body.

Rate of Urinary Elimination of Salicylate

The rate at which salicylate is eliminated through the kidneys was first studied by Blume and Breunig [1931]. They gave 250 mg. of sodium salicylate to rabbits and found that the average hourly

half of the total salicylate excreted in human urine was present as salicyluric acid.

The recent work of Kapp and Coburn [1942] leaves no doubt that salicyluric acid is not only one of the final metabolic products of salicylates but a major one. These investigators found that in normal human beings to whom sodium salicylate was given about half of the salicylate excreted in the urine is present as salicyluric acid. This observation was confirmed by the findings of Smith and his associates [1946] and of Lester, Lolli and Greenberg [1946].

In the passage of salicylates through the body the metabolic changes undergone may be summarized as follows: The salicylate esters are largely hydrolyzed in the gastrointestinal tract or after absorption, with the liberation of the free salicyl group. A small amount of the esters ingested may appear in the blood, and there is some suggestion but no definite certainty that a small portion may appear in the urine, unhydrolyzed. Of the free salicylate liberated or ingested as such, approximately 75 per cent is excreted in the urine as compounds containing intact salicyl groups; the remainder is presumably destroyed by oxidation with the formation of gentisic acid and other products of oxidation. Of the total amount of salicylate eliminated, approximately half is present as salicyluric acid, one-fourth as the sulfuric or glucuronic acid conjugates of salicyl acid, and one-fourth as free salicylate.

ELIMINATION

Following the ingestion of salicylates, small amounts may appear in the feces (140, 1476, 2162, 3351, 3774), sweat (512, 796, 1476, 2370, 2723, 3427, 4077), saliva (89, 512, 644, 1066, 1067, 2370, 2723), milk (489, 796, 1984), and bile (644, 796, 3079). The elimination in these media is insignificant compared to that in the urine.

Total Amount of Salicylate Eliminated in the Urine

After the ingestion of 1.9 to 3.0 g. of sodium salicylate, Mosso [1889] recovered from the urine amounts which, by his method of analysis, represented 96.8 to 106.7 per cent of that administered. In a dog given 250 mg. per kg. he recovered 102.1 per cent. Although Hanzlik and Wetzel [1920 (1481)] recovered only 23 to 37 per cent of salicylate in the urine after giving methyl salicylate to four dogs and one cat, Hanzlik, DeEds and Presho [1922]

It is now well established that there is no renal threshold for the excretion of salicylate. This fact was first suggested by Hérissé, Fiessinger and Debray [1922]. Fiessinger and Debray [1922] supported this suggestion by demonstrating that salicylate appeared in the urine even when the concentration in the blood was less than 1 mg. per 100 cc.

Chabanier, Lebert and Lobo-Onell [1923 (621)] obtained values for renal clearance of salicylate, based on the total salicylate concentration in the plasma, so small that they concluded that the major portion of the plasma salicylate was protein-bound and does not clear the kidney. Only the unbound salicylate passes the kidney with a clearance value approximately the same as that of urea.

The views of these investigators were supported by the observations of Lester, Lolli and Greenberg [1946]. They determined, by direct analysis of the plasma for protein-bound and unbound salicylate, that the clearance of unbound salicylate was similar to that of urea both in normal and rheumatic subjects.

Duration of Salicylate Excretion

The duration of excretion of salicylate is dependent on the amount given and on the rate at which the body disposes of salicylate by oxidation and elimination. From the numerous observations reported in the literature, in which the amounts of salicylate taken and the duration of excretion are recorded, an approximate relationship between the two may be obtained. The data from these reports are assembled in Table 9. Although the observations were made on ill as well as healthy subjects, and a variety of salicylate compounds was given, it may be seen that the excretion of salicylate starts within a short time after its administration and with small doses lasts for $\frac{1}{2}$ to $1\frac{1}{2}$ days but with large doses may continue for 6 to 10 days.

The relationship between the amount of acetylsalicylic acid ingested and the time required for completion of urinary elimination in healthy human subjects was determined by Lester, Lolli and Greenberg [1946]. Doses of 0.33, 0.65, 0.98, 1.30, 1.63 and 1.95 g. were given. The duration of excretion for each of the doses is shown in Figure 16.

The comparative duration of excretion of salicylate after the administration of different salicylate compounds has not been extensively or recently studied. Filippi [1899] and Brunner [1900]

elimination during the first 6 hours after administration was 40.8, 41.3, 15.0, 8.2 and 5.4 mg. of salicylic acid. Thus more than 40 per cent of the salicylate was excreted within 6 hours. After giving 60 to 100 mg. of sodium salicylate per kg. to children Kapp and Coburn [1942] found that not more than half was excreted in 24 hours. After intravenous administration of 1.25 g. to a 13-year-old boy, 30 per cent was excreted during the first 12 hours and 30 per cent during the second 12 hours. Lester, Lolli and Greenberg [1946] determined the hourly rates of excretion of salicylate in the urine after administration of 0.33, 0.98 and 1.95 g. of acetylsalicylic acid to normal subjects. Their findings are shown in Figure 15. Excretion was virtually complete 15, 20 and 30 hours after administration of the respective doses. From the hourly values indicated on the curves in Figure 15 it is possible to compute the proportion of the ingested salicylate excreted at any time.

Additional data regarding the rate of urinary elimination of salicylate have been reported in studies concerned with the effect of alkalis and acids on elimination. These will be discussed shortly.

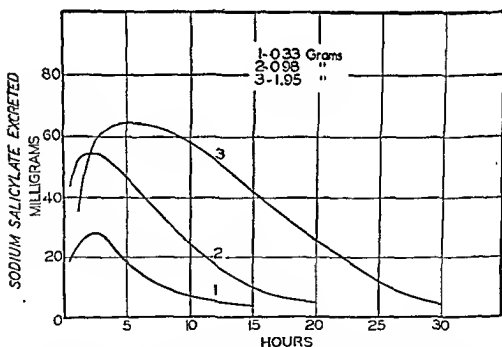


FIGURE 15.—Excretion of salicylate (as sodium salicylate) per hour after ingestion of acetylsalicylic acid. Reproduced from Lester, Lolli and Greenberg (2103).

	<i>Subject</i>	<i>Dose</i>	<i>Recorded Start</i>	<i>Recorded End</i>
<i>Calcium acetylsalicylate</i>				
Dellamartina (835)	Human	0.5 g.		11-12 hr
<i>Salicylsalicylate</i>				
Hanzlik & Prescho (1471)	Human	1.0 g.		42-72 hr.
Hanzlik & Prescho (1471)	Human	4-12 g.		96-138 hr.
<i>Methyl salicylate</i>				
Hanzlik & Prescho (1472)	Human	1.2 g.		51-74 hr.
Hanzlik & Prescho (1472)	Human	6.6-10.7 g.		62-120 hr.
<i>Ethyl salicylate</i>				
Houghton (1668)	Human	1 cc.	30-45 min.	10 hr.
<i>Ammonium salicylate</i>				
Johnson & Hanzlik (1781)	Human	4 g.		2 days
Johnson & Hanzlik (1781)	Human	10-14 g.		3-6 days
<i>Novaspirin</i>				
Pinczower (2744)	Human	1.6 g.	10-15 min.	28-33 hr.
<i>Salol</i>				
Pinczower (2744)	Human	1.55 g.	20 min.	30-33 hr.
<i>Salipyrine</i>				
Pinczower (2744)	Human	2.35 g.	25 min.	29-32 hr.
<i>Calcium acetylsalicylate</i>				
Thompson & Dragstedt (3479)	Human	0.6 g.	32 min.	33 hr.
<i>Diplosal</i>				
Tocco (3496)	Dog	10-25 mg./kg.		72 hr.
Tocco (3496)	Rabbit	70-100 mg./kg.		22-23 hr.

observed that in dogs, frogs and man, acetylsalicylic acid is eliminated over a longer period of time than equivalent amounts of sodium salicylate. Manasse [1900 (2291)] found that in man the urinary excretion of salicylate lasted longer after 1 g. of acetylsalicylic acid than after the same amount of salicylic acid. Lehman [1907] observed durations of salicylate excretion of 20 to 30 hours and 48 hours, respectively, following the ingestion of equivalent amounts of acetylsalicylic acid and methylene citrylsalicylic acid.

TABLE 9.—*Duration of Urinary Elimination of Salicylates*

<i>Salicylic acid</i>	<i>Subject</i>	<i>Dose</i>	<i>Recorded Start</i>	<i>Recorded End</i>
Chelchowski (647)	Human	1.25 g.		30-47 hr.
Chopin (662)	Human	1.0 g.	15 min.	38 hr.
Ingria (1711)	Human	0.25 g.	22-24 min.	6 hr.
Manasse (2291)	Human	1.0 g.	30 min.	7 hr.
Nelson (2540)	Human	10-20 g.	4-10 min.	2-3 days
Pinczower (2744)	Human	1.0 g.	10 min.	29-39 hr.
Balz (149)	Human	5.0 g.	3 min.	50 hr.
Brugsch (465)	Human	5.0 g.		2-3 days
Hanzlik, Scott & Thoburn (1476)	Human	13.0 g.		74-80 hr.
Hanzlik, Scott & Thoburn (1476)	Human	14.0 g.		68-110 hr.
Hanzlik, Scott & Thoburn (1476)	Human	12.0 g.		80-110 hr.
Loberg (2180)	Human	270 mg./kg.		21-32 hr.
Petersen (2716)	Human	26.0 g.		10 days
Pinczower (2744)	Human	1.0 g.	10-15 min.	33-37 hr.
Taltavull & Maurelli (3435)	Human	2.0 g.		20-37 hr.
Taltavull & Maurelli (3435)	Human	18.0 g.		64-72 hr.
Taltavull & Maurelli (3435)	Human	23.0 g.		47-68 hr.
<i>Acetylsalicylic acid</i>				
Block (329)	Human	0.2 g.		68 hr.
Block (329)	Human	0.4 g.		73 hr.
Chidichimo (650)	Human	10 mg./kg.		10-12 hr.
Dreser (930)	Human	1.0 g.	22 min.	12 hr.
Gazert (1244)	Human	1.0 g.	15 min.	17-19 hr.
Gazert (1244)	Human	3.0 g.		20-32 hr.
Hanzlik & Presko (1470)	Human	4.0-15.0 g.	10 min.	72-144 hr.
Hill (1609)	Human	1.0 g.	20-38 min.	19-29 hr.
Hill (1609)	Child	0.3 g.	16-20 min.	17-18 hr.
Manasse (2291)	Human	1.0 g.	70 min.	7 hr.
Pinczower (2744)	Human	1.3 g.	10 min.	30-33 hr.
Stutzman, Orth & Mellish (3394)	Human	0.6 g.		18-24 hr.
Thelen (3462)	Human	1.0 g.	15-20 min.	18 hr.
Thompson & Dragstedt (3479)	Human	0.6 g.	81 min.	26 hr.
<i>Soluble aspirin</i>				
Bercke (257)	Human	0.5 g.	30-45 min.	48-72 hr.
Bercke (257)	Human	5.0 g.	20-45 min.	2-3 days
<i>Hydroxyrinc grifa</i>				
Burow (505)	Human	0.5 g.	20 min.	4 hr.

ination normally continued for 3 to 4 days but that when moderate amounts of alkali were given the time of elimination was shortened to $2\frac{1}{2}$ to 3 days. In two subjects given large amounts of sodium bicarbonate the elimination was complete in 36 hours. A dog was given 4 g. of sodium salicylate alone on two separate occasions and with sodium bicarbonate on two others; when the urine was acid, salicylate elimination lasted for 96 and 120 hours but when the urine was alkaline it lasted 36 and 72 hours.

Hanzlik, Scott and Thoburn [1917 (1475)] reported that bicarbonate was without effect on the excretion of salicylate but are alone in this finding. Poller [1931] confirmed the earlier findings that the elimination of salicylate was more rapid when given with sodium bicarbonate, and Morris and Graham [1931] reported as much as a two- to threefold increase in the excretion in men after giving sodium bicarbonate.

Myung [1938] found that rabbits given sodium salicylate excreted an average of 37 per cent in the urine in 6 hours. When hydrochloric acid was given at the same time, only 10 per cent was excreted in this period but when sodium bicarbonate was given, 93 per cent was excreted. These investigators also found that chloral hydrate, urethane, morphine or heroin decreased the rate of excretion of salicylate in rabbits, the amount of decrease depending on the extent of narcosis.

Smith [1945 (3272)] and Smith and his associates [1946] found a significant relationship between the hydrogen ion concentration of the urine and the rate of salicylate excretion. As may be seen in Figure 17, the clearance of free salicylate increases sharply with increasing alkalinity of the urine.

Caravati and Cosgrove [1946] showed in five rheumatic patients that the urinary excretion of salicylate was increased an average of 51 per cent after giving sodium bicarbonate. Lowering the pH of the urine by the administration of ammonium chloride resulted in a prompt decrease in the excretion.

Lester, Lolli and Greenberg [1946] also found, in normal human subjects given 2.6 g. of acetylsalicylic acid, that sodium bicarbonate markedly increases the rate of salicylate excretion. These investigators suggested two possible explanations for this action of bicarbonate: (1) an increase in the unbound salicylate fraction in the plasma; or (2) a decrease in the tubular reabsorption. Either process would lead to an increase in the excretion of salicylate.

Daily Urinary Elimination of Salicylate During Prolonged Administration

Recent interest in maintaining an adequate concentration of salicylate in the blood for maximum therapeutic effect has led to some study of the amounts of salicylate lost from the body each day during a regimen of daily administrations of the drug. Odin [1932] found that the amount of salicylate excreted in the urine of subjects receiving 6 g. per day varied from 1 to 3.5 g. each day. In two subjects receiving daily 50 mg. of salicylate per kg. Kapp and Coburn [1942] observed that about half this dose was excreted each day.

Effects of Alkalis and Acids on Urinary Elimination of Salicylate

The marked effect that alkalis and acids have on the urinary excretion of salicylate has been a frequent observation. Ehrmann [1907] found that after ingestion of 5 g. of sodium salicylate elim-

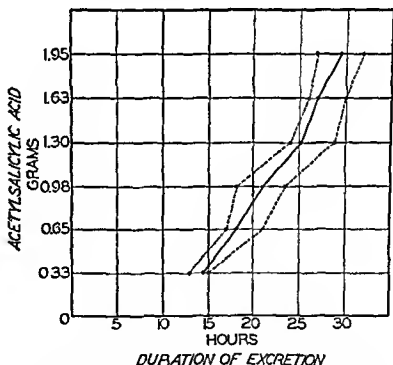


FIGURE 16.—Duration of excretion of salicylates after administration of acetylsalicylic acid to healthy humans. Broken lines, extremes of duration of excretion; solid line, average. Reproduced from Lester, Lolli and Greenberg (2103).

individuals, compared with 60 per cent in rheumatic fever patients. Examination of the individual data of this report, however, reveals a serious overlapping of results. Hanzlik and Preshe [1925 (1471)] measured the amount of salicylate eliminated in the urine in rheumatic fever patients given 4 to 12 g. of salicylsalicylic acid and in normal subjects given 1 g. The patients eliminated 55 to 72 per cent; the normal subjects 63 to 75 per cent. In other experiments these investigators (1472) determined the elimination of salicylate in rheumatic patients and in normal subjects after administration of methyl salicylate. The patients eliminated 40 to 76 per cent and the normal subjects 45 to 57 per cent.

Although the results reported by Hanzlik and his associates are indecisive, the observations of subsequent investigators indicated more clearly that in rheumatic fever the amount of salicylate eliminated is diminished.

Lodenkämper [1936 (2183)] gave calcium acetylsalicylate to two normal subjects, three rheumatic patients, and two patients with other diseases. The normal and nonrheumatic subjects eliminated 25 to 65 per cent; the rheumatic patients eliminated 9 to 28 per cent.

Kapp and Coburn [1942] reported that patients with rheumatic fever who responded well to salicylate and whose temperatures decreased rapidly to normal showed a diminished output of salicylate for only a few days, the amounts excreted thereafter being within the normal range. Patients in whom the fever was not reduced by salicylate showed diminished salicylate elimination for long periods. This suggested to the investigators that fever itself might be responsible for the diminished elimination of salicylate. In support of this conclusion they showed that three febrile non-rheumatic patients excreted subnormal amounts of salicylate.

Bauer [1944] found that patients with acute rheumatic fever receiving 5 to 10 g. of salicylate daily eliminated 39 per cent in the urine; that nonrheumatic patients receiving 2 to 8 g. of salicylate daily eliminated 81 per cent; and that normal, healthy individuals receiving the same amount eliminated 90 to 97 per cent.

Effects of Other Diseases and of Age on Urinary Elimination of Salicylate

Chopin [1889] found that normally after the ingestion of 1 g. of salicylic acid elimination starts within 15 minutes and lasts for

Smith and his associates [1946] found that the total excretion of salicylate after the ingestion of acetylsalicylic acid alone, with sodium bicarbonate, or with ammonium chloride, was essentially similar.

Effect of Rheumatic Fever on Urinary Elimination of Salicylate

As early as 1880 Squire noted that in rheumatic fever the excretion of salicylate appeared to differ from that in other conditions. Hanzlik, Scott and Thoburn [1917 (1476)] found that an average of 75 per cent of ingested sodium salicylate was excreted in normal

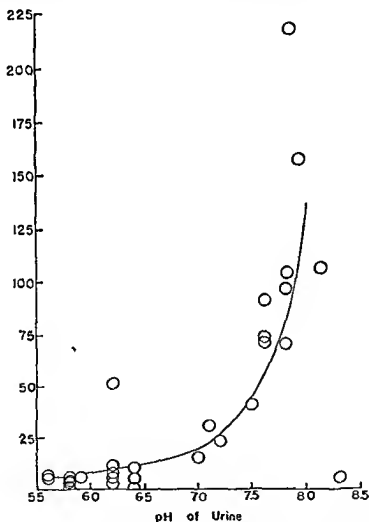


FIGURE 17.—Relationship between urinary pH and renal clearance of free salicylate. Reproduced from Smith, Gleason, Stoll and Orgorzalek (3274).

ADDITIONAL REFERENCES

Absorption:

115, 221, 367, 470, 534, 680, 728, 923, 932, 941, 1202, 1219, 1348, 1518, 1529, 1569, 1668, 2129, 2160, 2183, 2331, 2593, 2723, 2954, 3020, 3072, 3246, 3277, 3289, 3390, 3418, 3781, 3924, 3993.

Concentration in the body:

621, 680, 796, 879, 1005, 1066, 1249, 1341, 1364, 1465, 1476, 1567, 1571, 1823, 1905, 2127, 2183, 2421, 2602, 2641, 2723, 3250, 3351, 3367, 3437, 3449, 3496, 3633, 3634, 3916, 4077.

Elimination:

91, 120, 133, 139, 144, 256, 284, 334, 336, 372, 377, 432, 451, 485, 644, 932, 1005, 1249, 1341, 1460, 1465, 1478, 1647, 1845, 1955, 1983, 2077, 2081, 2097, 2370, 2406, 2421, 2422, 2593, 2653, 2723, 2831, 2836, 2923, 3012, 3072, 3082, 3233, 3289, 3467, 3691, 3781, 3817, 3836, 3978, 4077.

about 38 hours, and that 80 per cent is excreted. In patients with diseased kidneys the drug appears in the urine later, the time of elimination is prolonged and the amount excreted is diminished. Magi [1908] concluded from experiments that the rapidity of elimination of salicylates is related to the condition of the kidneys.

Hanzlik and Karsner [1917] produced different degrees of kidney damage in dogs by the intravenous injection of sodium salicylate. With only cloudy swelling of the kidney, 55.4 per cent of the administered salicylate was recovered in the urine but with acute tubular nephritis only 26.6 per cent was recovered. In three patients with nephritis Hanzlik and Wetzel [1920 (1480)] found only 54 to 65 per cent of ingested salicylate eliminated, compared with 72 to 92 per cent in normal individuals. They reported that the elimination of salicylate was likewise impaired in men suffering from chronic alcoholism, morphinism and hyperthyroidism but not in men with hepatic disturbances. In dogs and cats no change in salicylate excretion was produced by hepatic degeneration from administration of phosphorus.

Gaulier [1913] reported that the rate of elimination of salicylate was influenced by age: after the administration of 25 mg. per kg., the elimination lasted 18 to 22 hours in children of 5 to 10 years; 23 to 26 hours in those of 10 to 14 years; and 28 hours after the age of 14. Brouardel [cit. Heffter (1529)] reported, from his observations, that the onset and duration of excretion of salicylate depend on the age of the subjects. At the age of 23 years the onset was $\frac{1}{4}$ hour and the duration 1 day; at the age of 46 these values were, respectively, 2 hours and 2 days; at the age of 68, 48 hours and 8 days. According to Devrient [1921] the amount of salicylate eliminated is not influenced by age; but the amounts of salicylate he recovered in all subjects are so out of line with those found by other investigators as to render any conclusions uncertain.

It would appear from data reported in the literature that the amount of salicylate excreted is diminished in rheumatic fever particularly during the febrile stage. There is some evidence that the rate of excretion and amount excreted may be diminished as the result of damage of the kidneys. The rate of elimination appears to decrease with age.

subjects respond favorably to placebos. Such subjects must be excluded from test procedures or the findings will have little significance. (See Jellinek [1946].)

Experimental tests on man. Heinroth [1926] tested the analgesic properties of certain drugs by their influence on the response to faradic stimulation of the teeth. After oral administration of 1 g. of acetylsalicylic acid to two subjects the pain threshold, expressed in terms of units of current necessary to produce pain, increased from initial values of 62 and 119 units to 85 and 164. Hesse and Reichelt [1933], however, using a similar method, found that 0.5 and 1.0 g. of acetylsalicylic acid produced no measurable analgesic effect. Combinations of acetylsalicylic acid with codein, cinchophen, amidopyrine and phenacetin, as well as phenacetin alone, were slightly to moderately effective in increasing the pain threshold.

In 1934 and 1935 several doctoral theses were published by students of the dental schools in Münster, Germany (Düllmann [1934]; Ebbinghaus [1934]; Münchau [1934]; Strohschnieder [1935]), and at Halle, Germany (Vollrath [1934]), all dealing with measurement of the pain threshold by electrical stimulation of the teeth. Acetylsalicylic acid, aminopyrine, antipyrine, phenacetin and salicylic acid were reported as raising the threshold.

Mullin and Luckhardt [1935, 1937] employed the technique of von Frey to produce cutaneous pain with calibrated hairs. One-fourth of a grain of morphine or 75 cc. of alcohol increased the pain threshold markedly, while 50 gr. of acetylsalicylic acid had no effect.

For the measurement of pain threshold in man, Hardy, Wolff and Goodell [1940] determined the amount of radiant heat required to elicit cutaneous pain. A threshold rise of 35 per cent was reported after oral administration of 1.8 g. of acetylsalicylic acid. Schumacher and his associates* stated in the same year that the pain threshold, measured in this way, is uniform throughout the 24-hour day and is not affected by lethargy, tension and overirritability, or lack of sleep.

One year later Wolff, Hardy and Goodell [1941] published further data demonstrating the threshold-raising property of acetylsalicylic acid. The maximum rise in pain threshold attainable with

*Schumacher, G. A., Goodell, H., Hardy, J. D. and Wolff, H. G. *Science* 92: 110, 1940.

Pharmacology and Toxicology of Salicylates

ANALGESIC ACTION

THE salicylates have long been used effectively in the relief of certain types of pain, such as headache, myalgia and arthralgia. The way in which pain is alleviated by salicylate is unknown. Goodman and Gilman [1941] suggest that it "is probably due to a central depressant action located in the optic thalami. That the site of action is not cortical is indicated by the fact that analgesic doses of salicylate cause no mental disturbance, anesthesia or changes in sensation other than pain sense." The opinion has been expressed that the analgesic quality of acetylsalicylic acid depends on the presence in the blood of the unhydrolyzed ester (Stockman [1913]; Cambell [1921]; Cushny [1936]; Sollman [1936]; Davison [1944]). Some experimental support is given to this belief by Lester, Lolli and Greenberg [1946]. These investigators demonstrated the presence of appreciable amounts of acetylsalicylate in the blood of human subjects for 30 to 70 minutes after oral administration of 0.65 to 2.60 g. of the ester. They point out that clinical observations indicate that the period of analgesia corresponds only to that during which acetylsalicylate is present in the plasma, and that analgesia then ceases even though an appreciable concentration of free salicylate persists many hours longer.

There is, at present, no reliable laboratory method for measuring the effect on pain of small amounts of salicylate. Numerous investigators have reported methods of algometry in man, using mechanical, thermal and electrical stimulation. But the failure of most of these in the hands of others than the originators, together with the frequent reports in the literature of new methods for the measurement of analgesia, strongly suggest the inadequacy of any method as yet developed. In animal experiments, analgesia resulting from the administration of salicylate has been demonstrated only with large amounts of the drug. At present, reliable information concerning the analgesic action of small amounts of salicylate in man can be derived only from carefully conducted and controlled clinical tests on a large number of subjects. In such tests it is essential to use placebos for control since pain is highly subjective and many

The result of this pain was a marked elevation of the pain threshold of the teeth, lasting for several hours. Administration of 0.65 g. of acetylsalicylic acid before application of the cuff to the arm abolished the threshold-raising effect of the induced pain.

Goetzl [1946] recently reviewed and criticized the physiological bases and experimental methods used in algesimetric studies. He pointed out that in these studies the assumption is usually made that a change in pain threshold is a measure of the intensity of the analgesic action of a drug. That this assumption is not altogether correct is suggested by the fact that the reported effect or lack of effect from various drugs on pain threshold, as measured experimentally, has often failed to account for the analgesic effectiveness of the drugs observed clinically. The elevation of pain threshold, Goetzl believes, represents at most only one aspect of the analgesic action of certain drugs. He pointed out that an elevation of the pain threshold was reported in all tests in which heat was used as the pain stimulus but in only 11 per cent of the tests in which electrical stimulation was used. From the variable results reported, depending on the algesimetric method employed, Goetzl concluded that the apparent rise in pain threshold resulting from the taking of small doses of an analgesic drug is due primarily to the suggestibility of the subjects. Goetzl failed to observe, however, that all of the tests reported in man in which thermal stimulation was used were carried out by the same group of investigators, while the tests employing electrical stimulation were made by a number of investigators independently.

Tests on animals. Hesse [1930] studied the analgesic effect of various compounds on mice by the response of the animals to clamping of the proximal part of the tail and the anal mucosa. Sodium salicylate and acetylsalicylic acid up to lethal amounts did not produce analgesia. Toxic amounts of antipyrine, amidopyrine, phenacetin and acetanilid were necessary to obtain analgesia. Pohle and Spieckermann [1931] completely removed the response in mice to a hot needle lightly applied to the nose with administration of large amounts of aminopyrine and phenacetin but not with acetylsalicylic acid.

Macht and Macht [1940] determined, in rats, the voltage of a faradic current, applied to the scrotum, required to elicit pain. Fifteen to 60 minutes after the intraperitoneal injection of 10 mg. of sodium salicylate this voltage increased from an initial value of

this drug was 35 per cent and the smallest amount of acetylsalicylate producing this rise was 0.3 g.

Subsequently, Wolff and Goodell [1943] published results of experiments on the relation of attitude and suggestion to the perception of and the reaction to pain. They showed that hypnosis, noise, or repetition of digits may increase the threshold values and that a placebo given under such conditions that the subject believed it to be an analgesic might be followed by a rise in pain threshold. They further pointed out that the increased pain threshold from these causes may be higher than that reported as produced by acetylsalicylic acid. In all of their previous experiments on the analgesic effect of acetylsalicylate, in which ideal curves were constantly obtained even with small amounts of the drug, the factor of suggestion had not been given consideration and control with placebos was not employed. It is therefore possible that the validity of the results previously reported is open to question. In a later publication Wilker, Goodell and Wolff [1945] nevertheless accept the earlier data as valid.

Schumacher [1943] studied the effect of oral administration of acetylsalicylic acid on the pain threshold of skin having an ultraviolet erythema. The Hardy-Wolff method was employed for measurement of the threshold. Ultraviolet inflammation itself lowered the normal pain threshold by 25 per cent. This decrease was abolished by 0.6 g. of acetylsalicylic acid. The fact that a pain-relieving drug was taken was known to the subjects in these experiments and no placebo was employed; thus the question of suggestion again arises.

Burril, Goetzel and Ivy [1944] measured the pain threshold in human subjects by electrical stimulation of the teeth. Administration of 10 gr. of acetylsalicylic acid to 24 subjects resulted in changes in the pain threshold which were not significantly different from the variations obtained in control measurements.

Slaughter, Galt and Neff [1946] employed a modified Wolff-Hardy-Goodell method for comparing the analgesic properties of acetanilid and 5-bromoacetylsalicylic acid. The latter was reported to be twice as effective as the former.

Parsons and Goetzel [1946] studied the influence of acetylsalicylic acid upon the effect of induced pain on the pain threshold as measured by electrical stimulation of the teeth. Induced pain was obtained by means of a sphygmomanometer cuff inflated on the arm.

acetylsalicylic acid changed the pain threshold is certainly questionable.

Knowlton and Gross [1943] studied the influence of acetylsalicylic acid on the perception of pain caused by electrical stimulation of the skin of a dog. A pulsating current at a frequency of 200 per second and a pulse duration of 0.4 millisecond was applied for 0.5 second. The strength of stimulus, expressed in milliamperes, was measured by a cathode ray oscillograph. Widening of the eye was taken as an expression of pain. Forty milligrams of acetylsalicylic acid per kilogram raised the current required from an initial value of 2 milliamperes to a maximum of 7.

Kueter and Richards [1943] measured the electrical charge, applied to a wired cage bottom, required to increase movements of mice placed within the cage. Acetylsalicylic acid in doses of 500 mg. per kg. had no effect in altering the activity of the mice.

Smith, D'Amour and D'Amour [1943] focused the radiation from an incandescent lamp on the tip of the tail of the rat until a flipping of the tail occurred; this movement was taken as a sign of pain perception, and the time of exposure required was taken as a measure of the pain threshold. An arbitrarily designated increase in the pain threshold over that of untreated animals was taken as 100 degrees of analgesia. The effects of sodium salicylate, acetylsalicylic acid and mixtures of these with other analgesics are shown in Table 10. Inconsistencies in the results obtained cast doubt on the validity of this method of algesimetry. Thus acetylsalicylic acid or acetophenetidin alone had no effect when given subcutaneously, while the combination of the two resulted in marked analgesia. On the other hand, each of these drugs administered orally produced analgesia while a combination of the two did not. Similar inconsistencies, as seen in Table 10, occur with the other compounds administered. Using the same method for the measurement of pain threshold in 34 rats, Ercoli and Lewis [1945] observed no analgesia after oral administration of acetylsalicylic acid in doses ranging from 0.5 to 2.5 g. per kg.

Hart [1946] measured the analgesic potency of several compounds in rats, using the method of Smith, D'Amour and D'Amour. Arbitrarily assigning a value of 1 to the potency of acetylsalicylic acid, he reported that of salicylamide to be 7.5; di-iodosalicylamide, 5.3; sodium salicylate, 3.6; acetanilid, 2.6; o-acetylsalicylamide,

325 to 445. After oral administration of 30 mg. of acetylsalicylic acid or phenyl salicylate, however, no change was detectable.

Andrews and Workman [1941] measured the skin pain threshold in two dogs as the amount of radiant heat, expressed in watts, which elicits a pain response. In a series of such measurements one animal had a mean normal threshold value of 296 watts with extremes of 330 and 260; the other animal had a mean of 279 watts with extremes of 290 and 260. Thus, variations of approximately 24 and 12 per cent were found in measuring normal thresholds. Administration of 85 mg. of acetylsalicylic acid per kg. was then described as raising the threshold approximately 12.5 per cent. The curve representing this rise and the individual measurements from which it was constructed are shown in Figure 18. From the variations in normal threshold found by these investigators, and from the curve constructed from the individual measurements, the extent to which

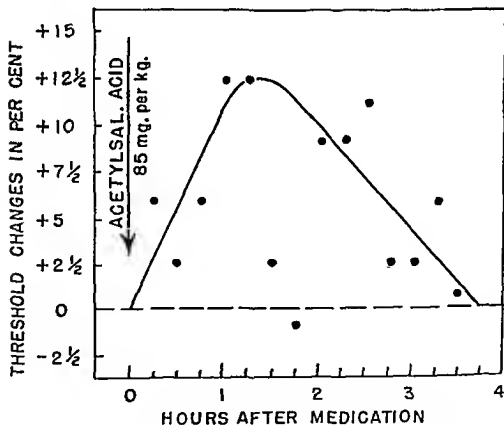


FIGURE 18.—Pain threshold changes in dogs after acetylsalicylic acid. Based on Andrews and Workman (75).

Hildebrandt [1933] estimated the effect of acetylsalicylic acid on the pain threshold of guinea pigs by thermal stimulation of the skin. A dose of 100 mg. of acetylsalicylic acid per kg. had no effect; with 200 mg. per kg., four of seven animals showed a marked decrease in sensitivity to pain while three showed no change.

Albright [1939] produced pain in cats by applying pressure to the tail. The analgesic action of antipyrine and acetylsalicylate was found to be similar and less than that of aminopyrine.

The amounts of salicylate as well as of other drugs used in animal experiments to demonstrate analgesia are large and frequently toxic. Whether the results obtained indicate the analgesic effectiveness in man of therapeutic amounts is therefore open to doubt.

Clinical tests. Simon [1931] determined the analgesic action of acetylsalicylic acid in 45 patients who had constant pain from arthritis, neuritis and headaches. After 10, 15 and 20 gr. of acetylsalicylic acid, moderate to complete relief was obtained in 52, 41 and 63 per cent of the patients respectively. A combination of equal amounts of the salicylate and magnesium oxide was sometimes found to be more effective than the salicylate alone.

Lewy [1942] studied pain control in several hundred patients suffering continuous pain due to inoperable carcinoma or during puerperium. Acetylsalicylic acid was given alone and in combination with other analgesic drugs or with nonanalgesic drugs. The drug was administered every hour until relief from pain occurred. With repeated doses of 0.15 g. of acetylsalicylic acid, 75 per cent of the patients with pain from carcinoma obtained relief, as did also 84.5 per cent of the patients with post partum pain. Combination of acetylsalicylic acid with other analgesics was not found to be superior to equivalent amounts of salicylate alone. The addition of quinine and caffeine to acetylsalicylic acid increased the effectiveness of the salicylate. Although Lewy observed that in a group of 233 patients given placebos almost half experienced relief from pain, he failed to allow for the factor of suggestion in drawing conclusions concerning the effectiveness of the drugs tested.

That suggestion may be a significant feature in the response of human subjects to analgesic drugs has been clearly shown by Jellinek [1946]. In a group of 199 subjects suffering from frequent headaches he studied the number of times relief was obtained in each individual with 3 analgesic compounds designated as *A*, *B* and *C*,

2.4; m-acetylsalicylamide, 2.2; bromosalicylamide, 2.2; antipyrine, 2.0; acetophenetidin, 0.8; and aminopyrine, 0.6.

TABLE 10.—*Analgesia in Rats after Sodium Salicylate, Acetylsalicylic Acid and Mixtures with Other Antipyretics**

	SUBCUTANEOUS		ORAL	
	Dose (mg./kg.)	Degree of Analgesia	Dose (mg./kg.)	Degree of Analgesia
Acetylsalicylic acid	400	2	450	33
Acetylsalicylic acid	600	0	—	—
Sodium salicylate	300	0	520	8
Aminopyrine	150	11	450	31
Aminopyrine	300	64	600	28
Antipyrine	300	2	900	6
Antipyrine	600	39	—	—
Acetophenetidin	600	0	700	15
Acetophenetidin	—	—	900	24
Aminopyrine	150		300	
+Acetylsalicylic acid	200	32	400	0
Aminopyrine	100		150	
+Antipyrine	200		200	
+Acetylsalicylic acid	100	23	100	6
Aminopyrine	150		300	
+Sodium salicylate	300	31	500	0
Aminopyrine	150		225	
+Antipyrine	200		300	
+Sodium salicylate	300	59	450	46
Acetylsalicylic acid	300		500	
+Acetophenetidin	300	39	450	0
Acetylsalicylic acid	200		300	
+Antipyrine	300	5	300	11
Sodium salicylate			500	—
+Acetylsalicylic acid	—	—	500	2

*Data of Smith, D'Amour and D'Amour (3262).

Hesse, Roesler and Bühler [1930] observed that for several days after guinea pigs were given subcutaneous injections of 0.05 cc. of croton oil, the sites of injection were extremely sensitive and the animals squealed if touched lightly. No apparent analgesia was afforded by the administration of 750 mg. of sodium salicylate per kg. The administration of 1,000 mg. of this drug per kg. or of 400 mg. of acetylsalicylic acid per kg. resulted in good analgesia.

[1884] obtained similar results in dogs with doses of 0.5 to 1.0 g. of salicylic acid. Hare [1887] reported, however, that salicylic acid had little effect in dogs on fever produced by injection of pepsin. Gottlieb [1890] found that in rabbits with fever from "piqûre," doses of 260 and 300 mg. of sodium salicylate per kg. caused only a moderate drop in temperature. Hashimoto [1915] found only a slight reduction in temperature following the injection of 0.5 g. of sodium salicylate per kg. into rabbits and guinea pigs with fever from thermal stimulation of the heat-regulating center in the brain. Okumura [1938] observed that sodium salicylate was more effective in lowering a fever in 1-day-old than in 10-day-old rabbits.

Carré [1901] reported the successful antipyretic action of 1.0 to 1.5 g. of acetylsalicylic acid in rheumatic arthritis, pneumonia, endocarditis and tuberculosis. Renon [1902] administered acetylsalicylic acid in a variety of febrile conditions and found it to be the best and the least dangerous antipyretic drug, since he obtained effective relief from fever and observed no danger of collapse in his patients. Bondi and Katz [1911] produced a decrease in body temperature with acetylsalicylic acid in rabbits with fever from "piqûre."

Barbour [1919 (158)] observed a drop in temperature of 2° C. after giving 1 g. of acetylsalicylic acid to a patient with chronic tuberculosis.

Winter and Barbour [1928] gave subcutaneously 100 mg. of sodium salicylate per kg. to rabbits with fever from injection of hay infusion and found a fall in temperature. They also induced a fever in dogs by injection of hay infusion and gave 100 and 200 mg. of acetylsalicylic acid per kg. orally and observed a decrease in temperature of 1.7° C. in 4 hours. They found also that administration of magnesium chloride with either sodium salicylate or acetylsalicylic acid increased the antipyretic action.

Guerra and Barbour [1943] produced a marked drop in temperature with subcutaneous administration of 100 mg. of acetylsalicylic acid per kg. to monkeys made febrile by yeast injection.

Climenko [1936] studied the antipyretic action of a mixture of acetylsalicylic acid and magnesium oxide. He found that in rabbits with fever from injection of typhoid toxin, oral administration of 100 mg. of acetylsalicylic acid per kg. caused a fall in temperature but that none resulted from 50 mg. of acetylsalicylic acid per kg. and none from magnesium oxide alone. When 50 mg. of acetylsali-

and with a placebo consisting of calcium lactate. The analgesic efficiency of each compound was measured by the ratio of the number of headaches relieved to the number of headaches treated and was designated as the "success rate." Of the total number of subjects, 120 (60 per cent) consistently obtained relief from placebo one or more times during each observation period, resulting in a placebo "success rate" for the entire group of 0.52. In the subjects not reacting to placebo, a "success rate" of 0.88 was obtained for compound *A*, 0.67 for *B*, and 0.77 for *C*. In the subjects who reacted to placebo, the corresponding values were 0.82, 0.87 and 0.82. Thus, significant differences between the effects of compounds *A*, *B* and *C* were apparent only when suggestible subjects had been eliminated.

Krantz, Iwamoto and Farson [1946] summarized data obtained from 4 physicians in clinics and private practice who administered 5-bromoacetylsalicylic acid to patients. In approximately 300 patients this drug afforded prompt relief to about 80 per cent of the cases of common headache and muscular pains. In headaches accompanying menstruation it was ineffective.

Local anesthesia. There is no indication in the literature that salicylates exert any local anesthetic effects. Rhode [1921] found that sodium salicylate in 2- to 10-per-cent solution and acetylsalicylic acid in 1- to 7-per-cent solution produced only a slight local hyperesthesia when injected intradermally. Delphaut [1936] was unable to anesthetize the cornea of rabbits' eyes by local application of 10- and 15-per-cent solutions of sodium salicylate. Injection of 0.25 g. or more of sodium salicylate into the spinal fluid of rabbits did, however, result in some anesthesia.

ANTIPYRETIC ACTION

The effect of salicylates in lowering the temperature in fever is an ancient observation which has been supported by extensive modern clinical and experimental evidence. Although this antipyretic action is usually prompt and effective, normal temperatures are rarely affected by the salicylates.

The antipyretic action of salicylic acid in rabbits was studied as early as 1875 by Zimmermann. Fever was produced by the injection of putrid liquid. Oral administration of 0.1 to 0.5 g. of salicylic acid was followed by a marked drop in temperature. Bochefontaine

a corresponding dilution of the blood. The drop in temperature was attributed to this increase in water of the blood and the subsequently increased dissipation of heat by radiation and evaporation from the surface of the body. From experiments with dogs, Dodd, Minot and Arena [1937] concluded that salicylate causes an increase in both the production and dissipation of body heat, the increase of the latter being the greater. The preponderance of evidence thus favors the opinion that the antipyretic action of salicylate is due to an increased rate of heat dissipation.

The main support to the view that the antipyresis results from decreased heat production is given by Yoshinaga [1925] who, on administering 300 mg. of sodium salicylate or of acetylsalicylic acid per kg. orally to mice, found an average decrease in heat production of 27 per cent and an increase in heat dissipation of only 2 per cent.

EFFECT ON CARDIOVASCULAR SYSTEM

Effect on the heart. Many of the investigations of the effect of salicylate on the heart have been made on the perfused isolated organ. Friderichsen [1917] perfused the frog heart with Locke's solution containing 10, 20, 30, 40 and 50 mg. of sodium salicylate per 100 cc. A concentration of 10 mg. per 100 cc. had no evident influence; 20 mg. per 100 cc. caused a decrease in activity; 50 mg. per 100 cc. caused a further decrease, with cardiac arrest in 10 minutes. Using blood instead of Locke's solution, 100 mg. of sodium salicylate per 100 cc. caused a temporary and slight increase in the activity of the heart; 200 mg. per 100 cc. caused a decrease, with cardiac arrest in 30 minutes.

Salant and Johnson [1923] perfused the hearts of frogs and turtles with sodium salicylate, sodium acetylsalicylate, and methyl salicylate in Ringer's solution. A concentration of 50 mg. of sodium salicylate per 100 cc. had no effect on the heart; 100 mg. per 100 cc. caused a depression of cardiac activity and 200 mg. per 100 cc. produced heart block. With sodium acetylsalicylate, a concentration of 400 mg. per 100 cc. was required to cause any depression of heart action. A saturated solution of methyl salicylate, approximately 75 mg. per 100 cc., produced heart block in a few minutes.

In experiments with perfused frog hearts Mendenhall and Camp [1924] observed that only extremely high concentrations of acetylsalicylic acid depressed or stopped cardiac action. Concentrations

cylic acid per kg. was given with magnesium oxide the temperature fell.

Dreser [1899] failed to obtain any decrease in temperature in nonfebrile subjects following administration of acetylsalicylic acid, as did also Dodd, Minot and Arena [1937] in dogs. Birkofer [1939], however, observed a slight reduction of normal temperature in rabbits and monkeys given acetylsalicylic acid and dimethyl-acetylsalicylic acid.

Mechanism of Salicylate Antipyresis

It is generally agreed that the antipyretic action of salicylate is exercised primarily through the central nervous system and not by direct action of the drug on the peripheral blood vessels and sweat glands. Thus Isenschmid [1913] abolished the usual response of rabbits to salicylate by sectioning the brain stem behind the midbrain or the spinal cord at the 6th cervical vertebra. Dantas [1939] observed that acetylsalicylic acid, as well as other antipyretics, exercises its effect in dogs and rabbits by lowering the threshold of the thermal center, which was taken as the body temperature at which polypnea occurs. On the basis of the literature, Guerra [1944] concluded that the antipyretic action of acetylsalicylic acid is due to action of the drug on the hypothalamic nuclei.

Opinion has differed as to whether the action of salicylate on thermoregulation is in the direction of increasing loss of heat from the body surface or decreasing heat production.

Many investigators have found an increase of heat loss as the primary cause of antipyresis. In normal animals given sodium salicylate, Wood and Reichert [1880-82] observed an increased production of heat but an even greater dissipation of heat. Barbour and Devenis [1919] found that in normal human subjects receiving approximately 15 mg. of acetylsalicylic acid per kg., heat production increased approximately 6 per cent while heat dissipation remained unchanged with obviously no decrease in body temperature. In febrile subjects receiving 19 to 28 mg. of acetylsalicylic acid per kg., however, Barbour [1919 (158)] found that heat production changed little but heat dissipation increased an average of 38 per cent with a resulting drop in temperature.

In febrile dogs, Barbour and Herrmann [1920] and Barbour [1926] found that the administration of sodium salicylate produced a shift of water from the tissues to the blood stream with

bert administered sodium salicylate to frogs, guinea pigs and dogs and observed no disturbance in the action of the heart. Blanchier and Bochefontaine [1878], however, found that in dogs, massive doses of sodium salicylate changed the rate and rhythm of the heart, the organ finally stopping in diastole.

Able [1885] injected 8 to 32 drops of methyl salicylate into the jugular vein of cats and observed an acceleration of the pulse rate with the smaller doses and diminished pulse rate with the larger doses. A similar rise in pulse rate was observed in dogs given methyl salicylate orally (3778), and in dogs and rabbits given the compound intravenously and subcutaneously (644, 645).

Dreser [1899] reported that sodium salicylate decreased the pulse volume of the heart in frogs, while acetylsalicylic acid increased it. Harrass [1903] injected 0.125 to 0.25 g. of sodium salicylate subcutaneously into frogs. The heart rate was slowed, the contractions became weak, and the heart stopped after 10 to 15 minutes.

The action of ethyl salicylate on the heart of dogs was investigated by Houghton [1905]. He found that the vagus is stimulated by moderate amounts of this drug, causing a diminished heart rate; large doses exercised an intense local action on the heart muscle itself, resulting in complete paralysis.

Chidichimo [1905] gave acetylsalicylic acid orally to dogs and rabbits and found that after doses of 10 to 50 mg. per kg. a decrease in blood pressure and pulse rate occurred which lasted for 2 hours; after 200 mg. per kg. these effects lasted for 4 hours. Block [1909] reported a reduction in the pulse rate of a dog given 400 mg. of acetylsalicylic acid per kg. orally; 700 mg. per kg. produced first an increase and then a decrease in the pulse rate.

Friderichsen [1917] reported that in frogs a concentration in the blood of 400 mg. of salicylate per 100 cc. arrested the heart action; concentrations of 131 and 261 mg. per 100 cc. caused a diminished heart rate. In rabbits a concentration of salicylate of 120 mg. per 100 cc. of blood did not affect the heart; higher concentrations resulted in diminished heart rate.

Barbour and Devenis [1919] observed no changes in the pulse rate of five individuals each of whom was given 1 g. of acetylsalicylic acid orally.

Pichon [1924] observed no alteration of cardiac rhythm nor any extrasystoles in dogs given up to 1 g. of sodium salicylate

approximating those occurring *in vivo* during the therapeutic use of the drug, stimulated the heart. This stimulation occurred even after atropine was added to the perfusate, thus excluding the possibility of vagus effects. Although the investigators did not indicate the perfusate used, the buffer content of all conventional fluids used for perfusing the heart is sufficient to convert the amounts of acetylsalicylic acid used in these experiments to neutral salts.

Further evidence of a stimulating action of salicylate on the heart was reported by Modrakowski and Sikorski [1925]. Contractions of the isolated frog heart, arrested by perfusion with distilled water, acetylcholine or chloroform, could be restored by applying a solution of 10 per cent sodium salicylate to the surface of the heart.

Simon [1933] perfused frog hearts with acetylsalicylic acid using a modified Ringer's solution from which sodium bicarbonate was omitted, thus preventing the neutralization of the acetylsalicylic acid. A concentration of 2.5 mg. of acetylsalicylic acid per 100 cc. resulted in cardiac arrest, and Simon concluded that the drug has an intense toxic action on the isolated heart even in concentrations occurring in the blood of individuals taking therapeutic doses. This investigator failed to observe that in the absence of a neutralizing base in the perfusing fluid the acetylsalicylic acid would diminish the pH sufficiently to exert simply the effects of acidity, and that only a salt of acetylsalicylic acid can exist in the blood *in vivo*.

These features were demonstrated in the experiments of Johnston [1936]. He perfused frog and turtle hearts with solutions of sodium salicylate, acetylsalicylic acid and its sodium salt, and methyl salicylate. Concentrations of sodium salicylate above 50 mg. per 100 cc. caused depression of the heart; solutions of 100 to 400 mg. per 100 cc. decreased the amplitude of the heart beat by one-half. Acetylsalicylic acid was far more toxic, a concentration as low as 3 mg. per 100 cc. resulting in a decrease in the amplitude of the heart beat. Sodium acetylsalicylate, however, in a concentration of 100 mg. per 100 cc. did not affect the heart, indicating that the toxicity of the acetylsalicylic acid in such experiments is due to its acidity. A saturated solution of methyl salicylate stopped the heart "almost instantly."

The effects of salicylate on cardiac action in the intact animal, while less specific than those on individual organs, have a closer bearing on practical toxicology. In 1877 Bochefontaine and Char-

well as toxic doses of acetylsalicylic acid. Dreser [1907] found a decrease in blood pressure in cats after very large doses of methylene-citrylsalicylic acid given intraveneously.

Friderichsen [1917] found no effects of salicylate on the circulation of rabbits below concentrations in the blood of 120 mg. per 100 cc. Higher concentrations caused a fall in blood pressure. However, Mendenhall and Camp [1924] observed an increased blood pressure in cats after intravenous administration of large amounts of acetylsalicylic acid. Cerebral vasodilatation was observed by Berezin [1916] in rabbits given salicylic acid but Kühn [1922] stated that vasodilatation of the cranial vessels due to salicylate is followed by constriction. Miwa, Ozaki and Shiroshita [1928] gave sodium salicylate to rabbits intravenously and found that with doses larger than 80 mg. per kg. a temporary constriction of the brain vessels occurred and was followed by dilatation. After smaller doses only constriction occurred; after very large doses only dilatation. A vasoconstricting action of sodium salicylate was reported in cats also after small doses, 10 to 20 mg. per kg., by Guggenheimer and Fisher [1929].

Suzuki [1931] observed the action of sodium, potassium, lithium and calcium salicylate on the blood vessels in the mesentery of the mouse and frog. Low concentrations produced dilatation; medium concentrations produced first dilatation and then constriction; high concentrations produced only constriction. Similar effects of strontium salicylate in frogs were reported by Simon [1934].

It appears from the literature that the doses of salicylate used in therapy have no significant effect on the cardiovascular system. Although high therapeutic doses may cause some vasodilatation, only toxic amounts of salicylate depress the circulation. There is no evidence, experimental or clinical, that salicylate in general, or acetylsalicylic acid in particular, is injurious to the heart. The concentrations of salicylate causing injury to the perfused heart are considerably higher than those ever found in man.

EFFECT ON RESPIRATION AND ACID-BASE EQUILIBRIUM

No significant effects of small amounts of salicylate on the acid-base equilibrium of the blood or respiration have ever been reported. Marked changes in both of these, however, have frequently been observed from toxic amounts of salicylate in experimental animals and in man. The most typical clinical symptoms of salicylate

intravenously. During continuous intravenous infusion of sodium salicylate, changes in the action of the heart became apparent when 4.75 g. had been given; after 5.7 g. the heart rate diminished, the contractions became weaker, and extrasystoles occurred. When 6.7 g. had been given, death occurred. Pichon concluded that cardiac activity is unaffected in the therapeutic use of salicylate.

Mendenhall and Camp [1924] measured in frogs the effect of acetylsalicylic acid on the threshold response of the heart to electrical stimulation. They observed a decreased threshold which they interpreted as indicating stimulation of the heart by the salicylate. From these observations and from their perfusion experiments, previously described, they concluded that acetylsalicylic acid has a direct stimulating effect upon the heart muscles which is not due to inhibition of the vagus mechanism, and that the drug depresses the heart muscle only in concentrations considerably higher than those ever occurring in the body.

Although Hanzlik, De Eds and Tainter [1925] reported an increase in the pulse rate in dogs after the intravenous administration of 490 mg. of sodium salicylate per kg., Dodd, Minot and Arena [1937] observed no such change after intravenous administration of 400 mg. of sodium salicylate per kg. in 5 hours or 1,500 mg. per kg. in 3 days, nor after the oral administration of 200 mg. of acetylsalicylic acid per kg. in 2 hours or 300 mg. per kg. daily for 3 days. Methyl salicylate administered subcutaneously in a dose of 800 mg. per kg. likewise caused no change in pulse rate.

The only report of damage to heart tissue was that of Madisson [1934] who observed fatty degeneration of the heart muscle in rabbits killed by intravenous injections of large amounts of methyl salicylate.

Effect on the circulation. Hare [1887] reported a marked increase in blood pressure in a rabbit given 56 mg. of salicylic acid per kg. orally and in four dogs given 12 to 23 mg. per kg. In rabbits, dogs and cats, after administration of sodium salicylate, Wiechowski [1902] also observed a rise in blood pressure with a dilatation of the peripheral blood vessels and a constriction of the intracranial vessels. Chatin and Guinard [1900 (644, 645)] reported a brief rise in blood pressure in dogs and rabbits after intravenous administration of small and moderate doses of methyl salicylate.

Chidichimo [1905] observed only a diminished blood pressure in dogs and rabbits after oral administration of therapeutic as

contrast to these observations Scott, Thoburn and Hanzlik [1917] and Hanzlik and Karsner [1917] found no change in the alkali reserve of the blood in man or in animals receiving large amounts of sodium salicylate. Johnson [1930] found no consistent change in the alkali reserve of animals given various salicylates; during 3 hours following the administration of the drug there was an increase in alkali reserve in some animals, a decrease in others and no change in still others.

An increase in the pH of the blood was found by some investigators in animals (903, 2856) and in man (1246). Others observed no change (1469, 1780, 3133). Hanzlik, De Eds and Tainter [1925] reported a marked decrease in the pH of the blood in dogs after administration of sodium salicylate, although Hanzlik and his associates, in two previous similar investigations [1917 (1469, 3133)], found no such change.

Finally, following the administration of large amounts of salicylate, marked alterations in the urinary excretion of acid or base have been observed, reflecting disturbances of the acid-base balance in the body. These alterations were evidenced as changes in the hydrogen ion concentration of the urine (71, 1246, 2602, 2659, 3010, 3566), changes in the titrable acidity of the urine (71, 2475, 2659, 3085), and changes in the urinary excretion of ammonia (71, 2659, 3085, 3566) and urea (2475).

One explanation offered for the observed effects of salicylate on respiration and acid-base equilibrium has been that this drug produces fixed acids in the body with a resulting acidosis. These acids are not products of the metabolism of the salicylate but, rather, acid products of a disturbed metabolism of the ordinary foodstuffs. Johnson [1930] administered large doses of sodium, ammonium, methyl and acetyl salicylate to cats and observed a marked increase in respiration with no consistent change in the carbon dioxide capacity of the blood. He concluded that there was a "fixed acid acidosis" compensated by a loss of carbon dioxide through an increased volume of breathing. The fact that there was an initial increase in respiration without a consistent decrease in the alkali reserve of the blood, however, strongly suggests that, contrary to the conclusions of Johnson, increased respiration in these experiments was not caused by an acid.

Morris and Graham [1931] gave 6 g. of sodium salicylate daily to nine children and observed a decrease in the carbon dioxide

intoxication—hyperventilation, vomiting and coma—are characteristic of disturbances of the acid-base equilibrium.

A number of investigators have reported the effects of large doses of salicylate on the volume of breathing but they did not explain the cause or result of these changes. Stimulation of respiration has thus been reported in animals after sodium salicylate (1468, 1489, 2525, 3794), acetylsalicylic acid (1780) and methyl and ethyl salicylate (6, 644, 645, 1989, 3778). On the other hand, depression of respiration has been reported after sodium salicylate (1489, 2056, 2277, 2364), acetylsalicylic acid (650, 2056), and methyl and ethyl salicylate (6, 1989). Some authors have reported the observation of both effects with the same drugs, depending upon the amounts given. In men Gebert [1931] observed no effect on respiration from 5 to 6 g. of sodium salicylate. It is not unlikely that all of the observations should be correct; moderately large amounts of salicylate may stimulate respiration while even larger amounts may depress it.

Variable effects of salicylate on an already altered respiration have also been reported. Thus sodium salicylate is said to prevent the depression of respiration by morphine in rabbits (2445). Acetylsalicylic acid, however, did not prevent the apnea produced in dogs by the injection of adrenalin or yohimbine (1519) nor did it have any effect on the hyperpnea of febrile monkeys (1385).

Besides its action on respiration, salicylate in large amounts has been observed to have an effect on the acid-base equilibrium. This effect is evidenced by a decreased carbon dioxide content of the blood, a diminished alkali reserve, an alteration of the pH of the blood and urine and a change in the urinary excretion of ammonia and urea.

A marked reduction in the carbon dioxide content of the blood was first observed by Walter [1877] in a rabbit given a large amount of salicylic acid. A similar effect of salicylate in animals was subsequently reported by a number of investigators and in man by many others (99, 177, 243, 408, 642, 727, 903, 1075, 1119, 1246, 1432, 1434, 1499, 1767, 2027, 2036, 2037, 2475, 2533, 2602, 2620, 2742, 2743, 2772, 3010, 3213, 3214, 3235, 3519, 3566, 3726).

A decrease in the alkali reserve of the blood following administration of large amounts of salicylate has also been reported in animals (524, 903, 3085) and in man (71, 524, 2602, 3010). In

sodium salicylate. They concluded that the increased respiration observed was not due to an acidosis but to the stimulating effect of salicylate on the respiratory center.

Gebert [1931] also observed a diminished carbon dioxide content of the blood and an increased pH of the urine in men given 5 to 6 g. of sodium salicylate. Although changes in respiration were often not recognized clinically, he concluded that salicylate stimulated respiration directly.

Odin [1932] determined the carbon dioxide content and pH of the blood and the acidity of the urine in 27 cases of salicylate poisoning in man and compared the values with those obtained in 150 diabetics in coma and precoma. This comparison indicated that the symptoms of salicylate poisoning were not, like those of diabetic coma, symptoms of acidosis. In 2 experimental subjects given large amounts of acetylsalicylic acid and sodium salicylate he observed hyperpnea, a decrease in the alkali reserve of the blood and an increase in the pH of the urine. Later, during the period of recovery, he observed a compensating acidity of the urine. He also concluded that salicylate has a direct stimulating effect on the respiratory center.

Although Dodd, Minot and Arena [1937] also found an increase in respiration, a rise in the pH of the blood and urine, and a decrease in the alkali reserve of the blood in dogs following the administration of large amounts of acetylsalicylic acid, sodium salicylate and methyl salicylate, they attributed the effects to an increased heat production and disturbances of the water balance in the body.

Andersen, Andersen and Brun [1941] administered acetylsalicylic acid to men and observed a decrease in the alkali reserve of the blood, a decrease in the urinary excretion of acid and ammonia, and an increase in the pH of the urine, indicating an alkalosis rather than an acidosis. After cessation of medication the alkali reserve returned to normal and the acidity of the urine increased temporarily above normal.

The occurrence of an alkalosis following administration of salicylate was further demonstrated by the observation of Ryder, Shaver and Ferris [1945]. A patient with rheumatic fever was given large amounts of sodium salicylate over a period of several days. On the sixth and seventh days hyperventilation occurred and the patient presented marked symptoms of alkalosis: the urine was

content of the plasma and in the excretion of urea, and an increase in the titrable acidity of the urine. The investigators concluded that an acidosis had developed.

Paisseau, Friedman and Vaille [1934] found a high acid and ammonia content in the urine, and a low alkali reserve in the blood, in a case of fatal poisoning by sodium salicylate, which they interpreted as indicative of acidosis resulting from this drug.

Cacciavillani [1942] concluded from experimental study that sodium salicylate causes a decrease of the alkali reserve in man and dogs due to formation of acetoacetic, lactic and phosphoric acids. Fashena and Walker [1944] observed an average decrease of 20 per cent in the carbon dioxide content of the blood of children receiving large doses of sodium salicylate. They postulated that this was due to the production of fixed acids in the body.

The similarity between the symptoms of severe salicylate poisoning and those of diabetic coma has given support to the concept that salicylate produces an acidosis. As early as 1906 Langmead observed an acetone odor on the breath, acetone in the urine and Kussmaul type of breathing in salicylate poisoning. Since then the presence of ketone bodies following large amounts of salicylate has been frequently reported (91, 99, 133, 134, 135, 136, 243, 642, 752, 903, 910, 1011, 1075, 1119, 1432, 1434, 1498, 1499, 1767, 1957, 2011, 2037, 2524, 2620, 2659, 2734, 2742, 2743, 2772, 2864, 2966, 3193, 3213, 3214, 3235, 3342, 3423, 3524, 3563a, 3772, 3835). Although an increase in ketone bodies is usually associated with acidosis, it is also known to occur after overventilation without acidosis and is explained by the theory that acetoacetic acid and oxybutyric acid resulting from normal fat metabolism are passed into the blood, instead of being burned, to aid in preserving the hydrogen ion concentration of the blood affected by the excessive loss of carbon dioxide. The increase in ketone bodies in the blood and urine under these circumstances would not be an indication of acidosis.

Hyperventilation would, in addition to these effects, cause others observed in salicylate poisoning: decrease in carbon dioxide content of the blood and in alkali reserve and increase in urinary elimination of alkali.

Veil and Graubner [1926] observed a decrease in the alveolar carbon dioxide tension, a decrease in the urinary ammonia, and an increase in the pH of the urine in man after the administration of

narily used therapeutically for analgesia, but only from large amounts as in the therapy of rheumatic fever or in poisoning.

EFFECT ON GASTROINTESTINAL SYSTEM

Functional disturbances of the gastrointestinal tract such as nausea, vomiting and epigastric distress, have frequently been observed during salicylate medication. That these gastric symptoms are not entirely due to a direct irritant action of salicylate on the mucosa of the stomach was first suggested by Wood [1902], who attributed them to an inhibitory action of salicylate on the digestive ferments, and later by Schmiedeberg [1913], who showed that the subcutaneous injection of salicylate in dogs caused vomiting.

Salicylic acid and sodium salicylate. Acute gastritis was observed by Manasse [1900 (2291)] in cats given salicylic acid orally. Vinci [1905] observed vomiting in a dog after an oral dose of 500 mg. of sodium salicylate per kg. The same effect was obtained in dogs by Waddell [1911] after parenteral administration of the drug. In two dogs with duodenal fistulas, Klocman [1912] found that 0.5 to 1.0 g. of sodium salicylate, given with a test meal, decreased gastric secretion by 50 per cent and also shortened the emptying time of the stomach. Eggleston and Hatcher [1915] attempted to determine the site of the emetic action of sodium salicylate in dogs by administering the drug intravenously. Vomiting occurred after 300 and sometimes after 200 mg. per kg. Eviscerated dogs made attempts at vomiting, indicating that the action of the salicylate was central.


In patients with rheumatic fever Caravati and Cosgrove [1946] frequently observed nausea, after intravenous as well as oral administrations of sodium salicylate, when a concentration of salicylate in the plasma of approximately 37 mg. per 100 cc. was attained. At no time after intravenous administration was any salicylate found in the gastric fluid, disproving the concept that the nausea and vomiting are due to the presence of salicylate within the gastric lumen.

Acetylsalicylic acid. The gastrointestinal disturbances resulting from acetylsalicylic acid are reported to be less severe than those of salicylic acid. Gazert [1900] concluded to this effect from his clinical observations. Gorges [1902] reported that acetylsalicylic acid was practically without effect on the gastrointestinal tract, and

alkaline, the pH of the blood was increased, the alkali reserve was diminished and tetany appeared. Twenty-four hours before death the urine suddenly became acid and the pH of the blood dropped. The occurrence of an acidosis shortly before death is common in many conditions terminating fatally and is not peculiar to poisoning by salicylate but is an indication of profound metabolic disturbance, probably asphyxial in nature.

A similar sequence of changes indicative of alkalosis was also observed by Rapoport and Guest [1945] in dogs and in a monkey. After repeated administration of large amounts of salicylate the carbon dioxide content of the blood diminished and the pH rose. The animals finally became moribund, at which time the pH of the blood began to fall.

A decrease of the carbon dioxide content of the blood and of the alkali reserve, following salicylate administration, has been, as indicated, a consistently uniform observation. The explanation for these phenomena, however, has been divided mainly between those who believe that salicylate produces an acidosis and those who believe that through respiratory stimulation it produces an alkalosis. Although a decrease in the carbon dioxide and alkali content of the blood may occur in both acidosis and respiratory alkalosis, some investigators have based their adherence to the acidosis concept solely on their observations of this change. A few others have, in addition, supported their beliefs on the finding of an increased urinary excretion of acids. Recent, more carefully controlled, clinical and experimental observations have revealed an initial increase in the excretion of base and an alkaline shift in the pH of the blood following salicylate administration. The variance between these findings and those of increased acid excretion may be explained by the fact that an acidosis does undoubtedly develop shortly before death in fatal salicylate poisoning and that also a decreased urinary excretion of base occurs during the period of recovery from salicylate poisoning. There is no valid evidence that salicylate causes acidosis except as a terminal condition in fatal poisoning. The preponderance of evidence is that the primary action of salicylate is to stimulate respiration directly; that ensuing hyperventilation results in a depletion of the carbon dioxide and a decrease in the alkali reserve, and hence the buffer substances of the blood, with the production of alkalosis. It must be borne in mind, however, that this action of salicylate is not exhibited from the doses ordi-



narily used therapeutically for analgesia, but only from large amounts as in the therapy of rheumatic fever or in poisoning.

EFFECT ON GASTROINTESTINAL SYSTEM

Functional disturbances of the gastrointestinal tract such as nausea, vomiting and epigastric distress, have frequently been observed during salicylate medication. That these gastric symptoms are not entirely due to a direct irritant action of salicylate on the mucosa of the stomach was first suggested by Wood [1902], who attributed them to an inhibitory action of salicylate on the digestive ferments, and later by Schmiedeberg [1913], who showed that the subcutaneous injection of salicylate in dogs caused vomiting.

Salicylic acid and sodium salicylate. Acute gastritis was observed by Manasse [1900 (2291)] in cats given salicylic acid orally. Vinci [1905] observed vomiting in a dog after an oral dose of 500 mg. of sodium salicylate per kg. The same effect was obtained in dogs by Waddell [1911] after parenteral administration of the drug. In two dogs with duodenal fistulas, Klocman [1912] found that 0.5 to 1.0 g. of sodium salicylate, given with a test meal, decreased gastric secretion by 50 per cent and also shortened the emptying time of the stomach. Eggleston and Hatcher [1915] attempted to determine the site of the emetic action of sodium salicylate in dogs by administering the drug intravenously. Vomiting occurred after 300 and sometimes after 200 mg. per kg. Eviscerated dogs made attempts at vomiting, indicating that the action of the salicylate was central.

In patients with rheumatic fever Caravati and Cosgrove [1946] frequently observed nausea, after intravenous as well as oral administrations of sodium salicylate, when a concentration of salicylate in the plasma of approximately 37 mg. per 100 cc. was attained. At no time after intravenous administration was any salicylate found in the gastric fluid, disproving the concept that the nausea and vomiting are due to the presence of salicylate within the gastric lumen.

Acetylsalicylic acid. The gastrointestinal disturbances resulting from acetylsalicylic acid are reported to be less severe than those of salicylic acid. Gazert [1900] concluded to this effect from his clinical observations. Görges [1902] reported that acetylsalicylic acid was practically without effect on the gastrointestinal tract, and

Roch [1912] observed less gastric disturbance from acetylsalicylic acid than from sodium salicylate. Vomiting has been reported in dogs, however, following the oral administration of acetylsalicylate, in doses of 200 mg. per kg. by Chidichimo [1905], 1,000 mg. per kg. by Barbour and Lozinsky [1923], and 600 to 1,000 mg. per kg. by Thompson and Dragstedt [1933]. Thompson and Dragstedt [1934] administered acetylsalicylic acid orally to dogs daily and all of them vomited when a total of approximately 0.6 g. per kg. had been given. Since the simultaneous administration of sodium bicarbonate or calcium gluconate resulted in fewer pathological findings in the stomach on autopsy but without having diminished the vomiting, these investigators concluded that emesis is due to a central action of salicylate. The immediate vomiting after a single large dose, they believed, might be due to local irritation.

The effect of acetylsalicylic acid and phenyl salicylate on the rate of gastric secretion in dogs was studied by Leichtentritt [1919]. Secretion was increased by both of the drugs. Schnedorf, Bradley and Ivy [1936] also reported changes in gastric secretion following the administration of acetylsalicylic acid in man, in normal dogs, and in dogs with Pavlov pouches. Single doses of 1 and 2 g. of acetylsalicylic acid in man caused a decrease in gastric evacuation and an increased titrable acidity of the gastric juice. In dogs, 1 g. of acetylsalicylic acid resulted in similar changes but of greater magnitude. Daily oral administration of 3 g. of acetylsalicylic acid to normal dogs for a month resulted in an increase in the titrable acidity of the gastric juice. Daily oral administration of 0.2 to 0.25 g. of acetylsalicylic acid per kg. for 3 weeks to dogs with gastric pouches resulted in marked increases in the volume of gastric juice and in acid secretion.

Paul [1943] observed gastric retention in man following the administration of acetylsalicylic acid and suggested that gastric distress experienced by some individuals after ingestion of this drug is due to pylorospasm.

Keith and Ross [1945] observed that gastrointestinal disturbances do not persist on continued use of the drug. In a group of patients with rheumatic fever given 10 to 13.3 g. of sodium salicylate or acetylsalicylic acid daily, about half experienced epigastric distress, nausea and vomiting, tinnitus, and deafness during the first few days of treatment; less than 10 per cent experienced these symptoms later.

Methyl salicylate. Gastric hypersecretion and vomiting after intravenous or subcutaneous administration of methyl salicylate and sodium methyl salicylate have been reported in dogs by Chatin and Guinard [1900].

Gastric Bleeding and Ulcers

Ulcers and evidence of gastric bleeding following the use of salicylates have been observed post mortem in fatal poisoning in men and in experimental animals. As early as in 1877 Bälz reported that salicylates produce nausea, vomiting and intestinal bleeding. Although Kobert [1906] stated that gastric disturbances such as inflammation and petechial bleeding after the ingestion of salicylates occur more readily in animals than in man, numerous autopsy reports on individuals who had taken large amounts of salicylate have shown hemorrhagic and ulcerative changes in the gastrointestinal tract (99, 134, 135, 136, 199, 208, 295, 787, 871, 900, 974, 1193, 1685, 1748, 1757, 2027, 2037, 2129, 2425, 2802, 3376, 3519, 3586, 3594, 3784, 3966).

An irritating and corrosive action of salicylate on the gastrointestinal tract has been reported after single as well as prolonged administrations of the drug. In 1899 Dreser stated that irritation and corrosion of the stomach mucosa occur from the local action of acetylsalicylic acid. Chistoni and Lapresa [1909] observed hyperemia and ulceration of the gastric mucosa in dogs given 150 to 200 mg. of acetylsalicylic acid per kg. orally and in rabbits given 600 to 700 mg. per kg. Edema and petechial hemorrhages in the gastrointestinal mucosa of dogs were found by Dodd, Minot and Arena [1937] after the administration of sodium salicylate intravenously, acetylsalicylic acid orally, and methyl salicylate subcutaneously. Busacchi [1938] reported that in a dog 200 mg. of acetylsalicylic acid per kg., and in a rabbit 700 mg. per kg., administered orally, caused ulcerations and punctiform hemorrhages of the gastric mucosa. Shimamura and Aoki [1939] observed gastric ulceration and hemorrhage in rats after oral administration of acetylsalicylic acid; in mice, only gastric hemorrhages were found, but no ulceration. Stutzman, Orth and Mellish [1941] gave single doses of 300 mg. of acetylsalicylic acid per kg. orally to rabbits, all of which had gastric ulceration 4 hours later. Leone [1916] reported that approximately 2 g. of methyl salicylate per kg., given to dogs hypodermically, caused no changes in the gastric mucosa,

while the same dose given orally caused swelling and hyperemia of the mucosa.

Douthwaite and Lintott [1938] investigated the action of salicylate on the gastric mucosa in man by means of gastroscopy. Sixteen subjects were each given 15 gr. of acetylsalicylic acid. In 12, marked hyperemia around adherent particles of the drug was observed, and in 1, submucous hemorrhage. In 2 subjects given salicylic acid the irritation was more intense. Calcium acetylsalicylate produced similar results in 1 of 5 subjects.

A patient who experienced gastric bleeding after taking small amounts of acetylsalicylic acid was examined gastroscopically by Hurst and Lintott [1939] who found that a few minutes after swallowing 2 tablets of the drug the gastric mucosa adjacent to them became intensely hyperemic and there was extravasation of blood. The gastric mucosa not in contact with the drug remained normal in appearance.

A possible explanation for the gastric bleeding observed gastroscopically was suggested by Honigsberger [1943] who pointed out that, in addition to direct irritation, acetylsalicylic acid in toxic doses may cause bleeding of the stomach mucosa indirectly as it has been observed to do in other organs.

Observations contrary to those of Douthwaite and Lintott were reported by Paul [1943] who made gastroscopic examinations of 107 subjects, each given 15 gr. of acetylsalicylic acid. No hyperemia, edema or hemorrhage was observed. In 5 subjects with benign ulcers of the lesser curvature, but without gastritis, there was no change after 10 to 15 gr. of acetylsalicylic acid. Twelve psychoneurotic patients with gastric distress showed normal gastric mucosae after administration of salicylate. Nine patients who had taken acetylsalicylic acid for a long period, 2 of whom complained of stomach distress after each administration, were examined gastroscopically by Paul. Except in 1 patient with a coincidental gastritis, the findings were negative.

Similar observations were reported by Caravati [1946] and Caravati and Crosgrave [1946]. Nausea and vomiting occurred in 12 patients receiving large doses of sodium salicylate intravenously and in 8 receiving it orally. On gastroscopic examination, however, the gastric mucosa in all of the patients appeared normal. Caravati concluded that the gastric symptoms during salicylate administration are probably due to the action of the drug on cerebral centers.

The conflicting observations following gastroscopic examination are difficult to explain. Although Paul attributed the positive findings of Douthwaite and Lintott to a high incidence of a nonspecific gastritis among their experimental patients, it is difficult to understand why there were no similar instances of nonspecific gastritis among their control subjects.

In studying the effects of prolonged administration of salicylate, Barbour and Fisk [1933] fed sodium salicylate to dogs for 2 to 4 weeks in daily doses of 300 mg. per kg. No gastric or duodenal ulcers developed. Thompson and Dragstedt [1934], however, found evidence of gastritis and ulceration in dogs receiving acetylsalicylic acid orally for 10 days; the effect was diminished when sodium bicarbonate or calcium gluconate was given simultaneously. Barbour and Dickerson [1938] gave acetylsalicylic acid orally and subcutaneously to rats daily and observed gastric ulceration after 10 days in 66 of 69 animals given 300 mg. per kg. per day. Subcutaneous administration of the same amount also resulted in severe gastric hemorrhages and ulcerations of the mucosa. When sodium bicarbonate was given with the salicylate, no hemorrhages were observed and the ulceration of the mucosa was less pronounced. An increase of the daily dosage to 500, 600 and 1,000 mg. per kg. increased the severity of the hemorrhages and ulceration. In contrast to these observations, Stutzman, Orth and Mellish [1941] found no ulcerations in 10 rats similarly given 300 mg. of acetylsalicylic acid per kg. orally each day for 10 days. In dogs, however, these investigators found that the oral administration of 200 mg. per kg. daily for 5 days caused gastric ulceration, while 25 to 50 mg. per kg. daily for 7 days did not.*

Relief of gastrointestinal symptoms by other drugs. Sodium bicarbonate is frequently used in conjunction with salicylate to prevent or diminish the gastric disturbance. Besides neutralizing any acid groups, which may be irritating, bicarbonate also hastens the emptying of the stomach, thus shortening the time of contact between the

*During publication of the present review the results of an investigation by Pauls, Wick and MacKay [1948] were published in which salicylate was observed to have a potent antiulcer action. In fasted rats, ligation of the pylorus resulted in ulceration of the rumen of the stomach. This ulceration could be inhibited, and in some instances entirely prevented, by the administration of certain substances. Sodium salicylate given intraperitoneally, subcutaneously or intravenously was found to have a strong antiulcer action, and acetylsalicylic acid was almost as active.

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it also occurs in other mucous and serous membranes and is related to disturbances of the prothrombin of the blood.

The way in which salicylate causes ulceration of the gastric mucosa is obscure. Observations that hyperemia may occur around adhering particles of the drug in the stomach suggest a local action of the drug but occurrence of inflammatory and ulcerative processes in the gastric mucosa after parenteral administration of salicylate excludes local action as the sole responsible factor.

EFFECT ON THE KIDNEYS

It has been observed in both experimental animals and man that large amounts of salicylate may cause renal impairment. Frey [1905] produced albuminuria in rabbits and dogs with salicylates. Vinci [1905] reported the occurrence of nephritis with albumin, white blood cells and casts in the urine of dogs and rabbits after administration of 0.4 g. of salicylate per kg. Repeated administration of 0.1 g. per kg. also produced nephritis while somewhat smaller doses caused only slight irritation of the kidneys. Ehrmann [1907] reported that after the administration of salicylic acid to rabbits albumin is more likely to appear if the urine is acid than if alkaline. For dogs, however, sodium bicarbonate appeared to increase rather than alleviate the albuminuria.

Chistoni and Lapresa [1909] examined the urine of dogs receiving 150 to 200 mg. of acetylsalicylic acid per kg. orally and rabbits receiving 600 to 700 mg. per kg. and found albumin, epithelial cells, hyaline casts, granulated casts and red and white blood cells. Histological examination of the kidneys revealed hemorrhages and pathological changes in the glomeruli, Bowman's capsule and the convoluted tubules.

Scott and Hanzlik [1916] after giving large doses of salicylate to dogs and cats, and Hanzlik and Karsner [1917] after giving 230 mg. of salicylate per kg. orally and subcutaneously to dogs, cats and rabbits, found albumin, leucocytes, casts and sometimes red blood cells in the urine. They found that salicylate in this amount intensified preexisting albuminuria and resulted in a decrease of renal efficiency as indicated by accumulation of nonprotein and urea nitrogen in the blood. Lesions of the kidneys were observed, varying in severity from simple cloudy swelling of the epithelium of the proximal convoluted tubules to extensive cloudy swelling of

salicylate and the gastric mucosa, and lowers the concentration of salicylate in the plasma, which has been shown to be a factor in the epigastric distress. Simon [1931] observed that the gastric irritation by salicylate is prevented by magnesium oxide. Schnedorf, Bradley and Ivy [1936] reported that calcium gluconate as well as sodium bicarbonate prevents vomiting in dogs after daily oral administration of 300 mg. of acetylsalicylic acid per kg.

Neither Barbour and Porter [1937] nor Schnedorf, Bradley and Ivy [1936] could prevent gastric ulceration due to acetylsalicylic acid in dogs by the use of calcium gluconate. Nor could Barbour and Dickerson [1938] prevent it in rats by using calcium gluconate, calcium carbonate or magnesium oxide. However, the latter investigators did decrease the severity of the ulcerations in rats with sodium bicarbonate. Busacchi [1938] found that the gastric mucosa of a dog and a rabbit remained normal when acetylsalicylic acid was given with equal amounts of sodium bicarbonate, and Shimamura and Aoki [1939] reported that gastric hemorrhage and ulceration in rats and mice due to acetylsalicylic acid were prevented by administration of sodium bicarbonate. Stutzman, Orth and Mellish [1941] found that calcium gluconate decreased the frequency and severity of ulcerations due to salicylate in rats, rabbits and dogs.

Caravati and Cosgrove [1946] gave sodium bicarbonate to patients being treated orally and intravenously with salicylate soon after nausea appeared. There was a prompt amelioration of the nausea and within 12 hours there was no gastrointestinal distress. They attributed this relief to a prompt reduction of the concentration of salicylate in the blood.

From the literature it may be concluded that large amounts of salicylate frequently cause nausea, gastric discomfort and vomiting; small therapeutic doses rarely do so. When such effects do occur after small doses, they are probably due to a local irritating effect on the gastrointestinal tract in sensitive individuals. After large doses the gastric symptoms are not due solely to local effects but also to a systemic or central action of the drug.

Bleeding from the gastrointestinal tract may occur in exceptional cases after small doses of salicylate and is probably due to an abnormal sensitivity. Bleeding, frequently observed after toxic doses of salicylate, is due solely to a systemic action of salicylates, since

PHARMACOLOGY AND TOXICOLOGY OF SALICYLATES

function as indicated by a diminished phenolsulphonephthalein excretion and an accumulation of urea nitrogen in the blood. These disturbances, according to these investigators, were not affected by the administration of sodium bicarbonate with the salicylates.

There appears to be general agreement in the literature that small amounts of salicylate such as are used for analgesia have no effect on the kidneys or on renal function. Large doses, such as those employed in the treatment of rheumatic fever, may cause renal impairment which disappears without residual damage after cessation of salicylate medication. Salicylates in amounts sufficient to produce poisoning may cause nephritis.

EFFECT ON THE LIVER

Balázs [1930] stated that urobilinogen in the urine, usually regarded as an indication of liver damage, is observed only after ingestion of large amounts of salicylate but enlargement of the liver has been reported by Bouvier [1912], Navarrete [1934], Huergo [1934], Charters [1944] and Desrochers [1945].

In a number of instances of fatal poisoning in man congestion and hyperemia of the liver have been observed (91, 134, 135, 2234, 2602, 3010, 3519) and in some, fatty degeneration has been reported (871, 1432, 1849, 2234, 2240, 2277, 2659, 2723, 2724).

Chatin and Guinard [1900 (645)] found congestion of the liver in dogs given lethal amounts of methyl salicylate or sodium salicylate subcutaneously or intravenously. In rabbits given large amounts of salicylsalicylic acid Tocco [1912] found the liver enlarged and Baldoni [1913] found diffuse tumefaction, interstitial hyperemia and small hemorrhages in the parenchyma of the liver. Hanzlik and De Eds [1926] reported a diminished permeability of the liver to "rose bengal" in a dog given 350 mg. of sodium salicylate per kg.

Barbour and Fisk [1933] gave sodium salicylate to dogs in doses of 400 to 600 mg. per kg. daily, and to dogs in doses of 100 to 200 mg. per kg. daily, and found congestion, vacuolization and fatty degeneration of the liver. Most of the dogs showed no marked retention of phenolsulphthalein.

Busacchi [1938] gave 235 and 285 mg. of acetylsalicylic acid to dogs and found no marked changes in the liver.

all of the cortical parts of the tubules; and, in some instances necrosis and desquamation.

Similar evidence of renal damage after large amounts of salicylate has been reported in dogs given sodium salicylate (90, 3497) and acetylsalicylic acid (168, 510, 3450, 3479); in rabbits given sodium salicylate (3497) and acetylsalicylic acid (510) and in rats given sodium salicylate (164).

Thompson and Dragstedt [1934], contrary to Ehrmann [1907], found less kidney disturbance in dogs when calcium gluconate or sodium gluconate or sodium bicarbonate was given with acetylsalicylic acid than when the drug was given alone. Barbour and Porter [1937], however, observed no alleviating effect of calcium gluconate in dogs, and Busacchi [1938] observed only a slight alleviating effect from sodium bicarbonate.

Lüthje [1902] found albumin, casts, and red and white blood cells in the urine of rheumatic patients soon after commencement of salicylate therapy. Klieneberger and Oxenius [1904] made similar observations in rheumatic patients but noticed that these symptoms disappeared although the salicylate therapy was continued. A similar temporary appearance of albumin and casts in rheumatic patients treated with sodium salicylate was also reported by Knecht [1904].

Frey [1905] observed that albumin and casts appeared in the urine of a healthy subject following the administration of 2 g. of sodium salicylate alone, but did not appear when a total of 27 g. of bicarbonate was given before and after the salicylate. He interpreted these observations as an indication of local irritation of the kidneys by free salicylic acid in the urine.

In patients with acute and chronic arthritis Ehrmann [1907] found albumin in the urine 12 to 24 hours after salicylate medication. Normal individuals, however, showed no albumin, or only traces, after 5 g. of sodium salicylate.

Following the administration of large doses of sodium salicylate to rheumatic and nonrheumatic individuals, Scott and Hanzlik [1916] found albumin, leucocytes and casts in the urine but observed no disturbance of renal function as judged from the phenolsulphonephthalein excretion test and the nonprotein nitrogen content of the blood. In two later reports, however, Hanzlik, Scott and Reyecraft [1917] and Scott, Reyecraft and Hanzlik [1917] stated that the administration of salicylate in large doses not only caused anuria, retention of water and edema, but also a decrease in renal

conditions observed a considerably increased flow of bile after doses of 1 g. of salicylic acid and 1 or 2 g. of sodium salicylate.

There is only one report in the literature of failure to obtain a cholagogue effect in a human being with a fistula which permitted measurement. Albu [1900] found no increase after administration of 5 g. of sodium salicylate on each of 2 consecutive days.

From the literature it is evident that damage to the liver occurs in poisoning by large doses of salicylate; that large therapeutic doses probably increase the flow of bile; and that small doses have no effect on the liver.

EFFECT ON THE AUDITORY ORGANS

Tinnitus and slight deafness are common symptoms of salicylate intoxication. In the treatment of rheumatic fever, prior to the routine clinical use of blood analysis to determine the concentration of salicylate present, the optimum rate of administration of salicylates was often judged by the appearance of these symptoms.

Disturbance in hearing following the use of sodium salicylate was first described by Muller [1877] who reported that a patient receiving 15 g. of sodium salicylate daily developed toxic symptoms including impairment of hearing. Scheyer [1902] reported deafness, tinnitus, vertigo and labyrinth disturbance in a patient treated with sodium salicylate. Four weeks after discontinuation of salicylate the symptoms had subsided considerably but were still present. Two instances of tinnitus and deafness were described by Schwabach [1904]. In one, due to sodium salicylate, deafness disappeared gradually but the tinnitus persisted for 5 years; in the other, due to antipyrine salicylate, both the tinnitus and deafness disappeared 4 weeks after discontinuation of the drug. Tinnitus from salicylate medication was reported by Seitz [1909]. Jackson and Pike [1922] reported an instance of impaired hearing in both ears in a patient who took acetylsalicylic acid daily as an analgesic after surgical treatment for adenitis. Hart [1931] described the case of a patient who was given 20 gr. of acetylsalicylic acid daily for 6 weeks, at which time tinnitus and deafness occurred. The acetylsalicylic acid was discontinued and instead 20 to 30 gr. of cinchophen were given daily. When 120 gr. of this drug had been taken the tinnitus had become more severe and deafness was profound. Rutin [1937] stated that he had observed many cases of

with dilatation of the portal veins was found in the livers of all the animals.

Lutwak-Mann [1942] reported that the respiration of liver slices was little affected in the presence of 0.8 per cent sodium salicylate but was appreciably inhibited by a concentration of 1.6 per cent. The glutathione content of the liver in rats was found to be greatly increased 24 hours after administration of sodium salicylate.

Stimulation of the secretion of bile by salicylates has often been reported clinically and in experimental animals. Thus Rutherford [1879] found 20 to 30 gr. of sodium salicylate to be a strong hepatic stimulant in dogs. Rosenberg [1890] observed an increased bile flow in dogs 30 to 45 minutes after the administration of 1 or 2 g. of sodium salicylate. Mandelstamm [1890] gave sodium salicylate to a dog with a biliary fistula and observed a slight increase in bile secretion after 1.5 g. and a 60 per cent increase after 3 g. From similar experiments Stadelmann [1896] concluded that sodium salicylate was a potent cholagogue; 75 to 125 mg. of the drug per kg. resulted in a slight increase in bile flow; 150 mg. per kg. increased the flow 60 to 70 per cent. Additional observations of this action of salicylate in dogs have been reported for sodium salicylate (919, 2378, 2611, 3295, 3331, 3740), acetylsalicylic acid (2378, 3079, 3295, 3331, 3740), phenyl salicylate (2378, 2611), methyl salicylate (2085), and 5-iodosalicylic acid (1836, 1837).

Some investigators failed to find an increased flow of bile in animals after the administration of salicylate. Thus Smyth and Whipple [1924] observed no increase after small doses of sodium salicylate in dogs with biliary fistulas. Stransky [1925] found no change in the secretion of bile in rabbits following intravenous injection of 0.1 g. of sodium salicylate or after the injection of 0.2 g. into the duodenum. Brugsch and Horsters [1923] not only failed to observe a cholagogue action of sodium salicylate in a dog, but found a decrease in the secretion.

Pfaff and Balch [1897] found that phenyl salicylate increased the secretion of bile in a woman with a biliary fistula. Moreigne [1900] reported an increased biliary excretion following sodium salicylate. In a patient with a biliary fistula, Ignatowski and Monosohn [1914] observed an increased secretion of bile after doses of 1.8 and 2.4 g. of sodium salicylate. Meiszner [1926] under similar

conditions observed a considerably increased flow of bile after doses of 1 g. of salicylic acid and 1 or 2 g. of sodium salicylate.

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permanent damage to hearing and to the cochlea due to salicylates.

Falbe-Hansen [1937] tested the acoustic and vestibular function of 41 patients receiving 3 to 8 g. of sodium salicylate daily. Thirty-three of the patients developed distinct auditory disturbances. In 10 patients there were vestibular symptoms as evidenced by spontaneous nystagmus. Several of the patients experienced dizziness which disappeared after the salicylate was discontinued. Permanent impairment of hearing was not observed.

Coleman [1934] expressed the opinion that acetylsalicylic acid may cause irreparable damage to the ears of susceptible individuals, and Taylor [1937 (3449), 1939] suggested that the use of salicylates by pregnant women may be one of the etiological factors in deafness of the newborn. Perner [1942] observed epistaxis and severe tinnitus in a patient with rheumatic fever after 3 days of daily administration of 8 g. of sodium salicylate. These symptoms were reported to have disappeared following the administration of 600 mg. of ascorbic acid.

Kirchner [1881] gave toxic doses of sodium salicylate repeatedly to rabbits, cats, dogs and guinea pigs and studied the effects on the ear. The cats, after 2 g. daily for 8 days, developed greatly increased sensitivity to sound. In all of the other animals hyperemia, ecchymoses and slightly red endolymph and perilymph were found at autopsy in the tympanic cavity. Blau [1904] administered sodium salicylate to mice, rabbits and guinea pigs and reported changes in the acoustic ganglion which were more severe in chronically poisoned animals than in those given the salicylate for only a short time.

After the administration of acetylsalicylic acid to experimental animals, Haike [1904] found hyperemia and bleeding in the tympanic cavity. The hemorrhages occurred only in those animals having convulsions or dyspnea before death, and since similar hemorrhages could be produced by suffocation or strychnine convulsions, Haike concluded that the bleeding in the ear was not due to salicylate but to the convulsions and dyspnea. Degenerative changes, however, were found in the spiral and vestibular ganglion and in the acoustic nerve itself. These changes varied from alteration in the staining properties to complete disintegration. Haike considered some of the changes as reversible. In an attempt to coordinate clinical and histopathological observations, he postulated that the tinnitus is due to irritation of the spinal ganglion; the

progressive changes lead to deafness and, by affecting the labyrinth, to vertigo.

Lindt [1913] gave 1.4 and 2.25 g. of sodium salicylate respectively to two guinea pigs. He observed no changes in the end organ of the acoustic nerve and no degenerative neuritis.

Covell [1936] gave 200 mg. of sodium salicylate per kg. daily for 3 to 8 weeks to rabbits, mice and guinea pigs. Three of the latter were pregnant. One cochlea from each animal, including the fetal, was examined histologically. All showed pathological changes, the most severe being in the fetuses. The significance of these observations is questionable in view of a subsequent report of Covell and Noble [1937] on similar experiments, also with guinea pigs, in which pathological changes were observed in the cochlea of animals receiving sodium salicylate and also the majority of control animals not receiving salicylate.

Mosher [1938] found hemorrhages in the cochlea of pregnant guinea pigs and their fetuses after salicylate administration but he showed that similar hemorrhages occurred in control animals due to trauma in preparation of the specimens or due to a rise in blood pressure.

Falbe-Hansen [1941] gave lethal doses of sodium salicylate to guinea pigs subcutaneously and found histological changes in the cells of the spinal ganglion and in the organ of Corti. He also pointed out that such changes may occur in control animals but the frequency of their occurrence was greater in the animals given salicylates.

Macht, Greenberg and Isaacs [1920] studied in men the effect upon the acuity of hearing, as judged by the distance at which a watch could be heard, of 5 gr. of sodium salicylate, 5 and 10 gr. of acetylsalicylic acid, and 5 and 10 gr. of phenyl salicylate. They reported that the acuity was decreased by about 25 per cent in all instances. Wilker, Goodell and Wolff [1945], however, found no change in the hearing threshold of six individuals after 0.3, 0.6 and 1.8 g. of acetylsalicylic acid when the test was made with an audiometer at frequencies of 128, 512, 2,048 and 9,747 cycles per second.

Falbe-Hansen [1939] studied the effect of sodium salicylate on the hearing of normal subjects and others with defective hearing and concluded that a single dose of 2 g. of sodium salicylate caused no symptoms. Three grams or more regularly caused some impair-

ment of hearing, tinnitus, sensations of intra-aural pressure, vertigo and spontaneous nystagmus. The deafness was described as of the sound conduction type. The duration of these symptoms was about 24 hours. The prolonged administration of 5 g. of sodium salicylate in divided daily doses produced the same symptoms but when the administration was discontinued the symptoms disappeared within 1 to 2 days. Individuals with defective ears reacted essentially the same as normal subjects except that in a few instances the symptoms lasted longer.

Falbe-Hansen's conclusion that the deafness due to salicylate was of the sound conduction type was disputed by Foght [1943] who described it as of the nerve deafness type. From experiments on 10 subjects given 8 g. of sodium salicylate each, Juul [1943] reached the same conclusion as Foght.

Although disturbances of the ear are characteristic symptoms of poisoning by large amounts of salicylate, there is no evidence, clinical or experimental, that small doses of salicylate, as used even repeatedly for analgesia, cause such symptoms or are injurious to the ear.

EFFECT ON TEETH AND BONES

Early textbooks (1073, 1905, 4000) mentioned an injurious effect on teeth attributed specifically to salicylate but the nature of the experiments from which these statements were derived does not justify the conclusions.

Von Mosengeil and Goltstein [1876] first reported an effect of salicylic acid on the teeth of dogs. Healthy teeth were drilled, the cavities filled with salicylic acid and covered with stopping material. Three days to a month later the cavities contained masses of detritus and the surrounding dentine was softened. Köster [1876] found that salicylic acid slowly dissolved the dental enamel and quickly destroyed the dentine, and Kunkel [1899], that teeth covered with moistened salicylic acid became soft.

Dott [1940] suspended healthy, noncarious teeth in 0.5-per-cent solution of acetylsalicylic acid and found that in 24 hours 16 mg. of calcium went into solution. Addition of sodium bicarbonate to the solution of acetylsalicylic acid prevented the solvent action.

Heinroth and Brauer [1941] observed rapidly progressing dental caries in an individual who drank a 4- to 6-per-cent aqueous suspension of acetylsalicylic acid several times daily for 5 months.

In vitro experiments carried out by them showed that a 4-per-cent suspension damaged teeth and that the crowns lost 20 to 37 per cent of their weight in 20 days in such a suspension.

Dott's observation that sodium bicarbonate prevents the effect of acetylsalicylic acid on the teeth indicates that the corrosive action observed by all of the above investigators is due simply to the acidity of the compounds used and not to any specific action of salicylate.

Only two experimental studies have been reported on the effect of salicylates on bone growth and structure. Mutch [1934] fed 500 mg. of acetylsalicylic acid per kg. to rats daily and found even with this large dose no decalcification of the bones. He did observe, however, an increased zone of calcification in the ossifying cartilage. Although this did not occur if calcium acetylsalicylate was administered, he nevertheless attributed it to the acetylsalicyl radical and not to acidity.

Benda and Debray [1939] injected 1 cc. of a 30-per-cent aqueous solution of sodium salicylate into the medullary space of one tibia in a rabbit. After several repetitions of this severe procedure the tibia became greatly enlarged with new unconsolidated bone material scattered through the middle and completely obliterating the ends of the medullary space.

EFFECT ON MUSCLES

Livon [1890] observed that after injection of 0.5 to 1.0 mg. of sodium salicylate subcutaneously to frogs, muscular activity as recorded on the myograph was first increased and later decreased. Von Fürth [1896] found that *in vitro* a 10-per-cent solution of sodium salicylate accelerated the coagulation of muscle myogen and—to a lesser degree—of myosin. Von Fürth and Schwarz [1909] reported that subcutaneous injection of 1 g. of sodium salicylate in cats diminished the paralyzing action of curare.

Hofmann and Rossi [1909] observed a permanent contraction of muscle *in vitro* suspended in 10- to 30-per-cent solutions of salicylate. Lower concentrations caused a transitory contraction. An increase in irritability was observed by Höber [1910] in frog muscle suspended in a 1.6-per-cent solution of sodium or lithium salicylate.

Schüller [1925, 1926] reported that sodium salicylate applied to muscles *in vitro* prevents the production of rigidity by caffeine

ment of hearing, tinnitus, sensations of intra-aural pressure, vertigo and spontaneous nystagmus. The deafness was described as of the sound conduction type. The duration of these symptoms was about 24 hours. The prolonged administration of 5 g. of sodium salicylate in divided daily doses produced the same symptoms but when the administration was discontinued the symptoms disappeared within 1 to 2 days. Individuals with defective ears reacted essentially the same as normal subjects except that in a few instances the symptoms lasted longer.

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of 250 mg. of sodium salicylate per kg. and oral administration of 250 and 500 mg. of acetylsalicylic acid per kg. resulted in an average increase of 48 and 25 per cent, respectively, in the concentration of sugar in the blood; in dogs with fever from coli vaccine similar dosages of these salicylates resulted in an average increase of 50 and 44 per cent in the concentration of sugar in the blood.

Ozu [1940] reported that in rabbits small amounts of sodium salicylate stimulate the parasympathetic nerves, increasing the secretion of the pancreas and the storage of sugar in the liver and thus diminishing the concentration of sugar in the blood. Large amounts of salicylate act directly on the liver causing glycolysis and hyperglycemia.

Lutwak-Mann [1942] injected large amounts of sodium salicylate subcutaneously in rats and observed no significant changes in the concentration of sugar in the blood. However, 4 and 7 hours after injection of the salicylate the liver glycogen dropped from an average of 2.86 per cent to 0.17 and 0.23 per cent, respectively. Such a remarkable change in liver glycogen due to the administration of salicylate needs further experimental confirmation.

There is good indication from the reported data that salicylate may alter the normal function of the liver in carbohydrate metabolism. Such disturbance of the stabilizing influence of liver function in the distribution and utilization of sugar in the body may well explain the contrasting clinical observations of both hyperglycemia and glycosuria and hypoglycemia and aglycosuria after salicylate administration. Whatever the effect of salicylate may be upon the urinary excretion of sugar, the general observations that this drug inhibits the storage and utilization of sugar in the tissues of the body militates strongly against its therapeutic use in large amounts in diabetes.

EFFECT ON NITROGEN METABOLISM

Clinical and experimental observations have suggested that the administration of substantial amounts of salicylate may have some effects on nitrogen metabolism. Observations on which this conclusion is based have dealt mainly with changes in the urinary excretion of uric acid, urea and other nitrogenous metabolites and to a less extent with changes in the concentrations of these substances in the blood following salicylate administration.

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In man, Menschel [1926, 1927] found that administration of 8 g. of acetylsalicylic acid prevented the occurrence of paralysis and rigidity of the brachioradial muscle as a result of chilling to 4° C. A similar effect of acetylsalicylic acid was observed by von Frey [cit. Eichholtz (1005)]; the drug restored activity to muscles made rigid by chilling; the pain due to chilling also disappeared.

The effect of acetylsalicylic acid on smooth muscle in dogs and rabbits was described by Chidichimo [1905]. Therapeutic doses given orally diminished contraction of the uterus while large amounts caused arrhythmia and irregularity. Thienes [1926], however, observed no effects of salicylate on excised strips of rabbit duodenum and uterus.

EFFECT ON CARBOHYDRATE METABOLISM

The earliest suggestion that salicylate alters carbohydrate metabolism emanated from numerous clinical reports, during the latter part of the last century, that the drug prevents diabetic glycosuria (190, 555, 985, 1353, 1835, 1913, 2427, 2503, 2566, 2589, 2590, 2714, 3008, 3457, 3727). Some observers pointed out, however, that this effect of salicylate resulted only after administration of large and frequently toxic amounts—10 to 12 g. per day—of the drug (190, 989, 1174, 1821, 2566, 3008, 3727). Salicylate was, nevertheless, used in the treatment of diabetes, although this use has long been discontinued.

In contrast to the early clinical observations that salicylate prevented glycosuria, hyperglycemia and glycosuria were found to be present in a number of more recently described cases of salicylate poisoning (642, 752, 1432, 1823, 2037, 2531, 2620, 2742, 2743, 2864, 2943, 2976, 2977, 3193, 3235, 3423, 3519). In only two cases of salicylate poisoning was hypoglycemia reported (1381, 1445). Moreover, Morris and Graham [1931] observed in rheumatic children that administration of salicylate results in an increase in the fasting concentration of sugar in the blood. They concluded that salicylate inhibits the utilization of glucose by the tissues and diminishes its storage in the liver. Starkenstein [1912] reported that the subcutaneous administration of 0.5 to 1.0 g. of sodium salicylate prevented adrenalin glycosuria in rabbits. Barbour and Herrmann [1921] found that in dogs the similar administration

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ditions (1442, 2401) and some observed no relationship between leucocytosis and uric acid excretion (2737, 3094).

Some doubt is cast on the concept that salicylate increases the production of uric acid in the body by the observations of Nagashima [1921]. In rabbits given salicylate, he found a decrease of uric acid in the blood occurring simultaneously with its increased excretion. Similar reductions in the concentration of uric acid in the blood following administration of salicylate were observed in men by other investigators (855, 1116, 1781).

Hall [1904] dismissed excessive nitrogen metabolism as the cause for increased uric acid excretion but offered the suggestion that the increase is due to a diminished destruction of uric acid by the tissues of the body as a consequence of salicylate administration. Stookey and Morris [1907], however, observed that liver, kidney, spleen and muscle tissue from animals given salicylate destroyed uric acid *in vitro* more rapidly than tissues from animals given no salicylate.

Still another explanation offered for the increased excretion of uric acid was that the administration of salicylate causes the kidneys to excrete uric acid more rapidly although its production in the body remains unchanged. Denis [1915 (854)] suggested that the increased excretion of uric acid in men following salicylate medication was due to a lowering of the threshold of the kidneys for this metabolite. This explanation for the increased excretion of uric acid is supported by the observations of Stern [1924] and of Yamaguchi [1931] who found that low concentrations of salicylate markedly increased the solubility of uric acid *in vitro*.

Data reported in the literature concerning the effect of salicylate on the excretion of nonprotein nitrogen compounds other than uric acid have been so variable as to justify no conclusions (11, 202, 854, 856, 1137, 1240, 1317, 1442, 1475, 1478, 1578, 1601, 1732, 1781, 2466, 2471, 2475, 2527, 2585, 2944, 2945, 3028, 3085, 3093, 3264, 3441, 3643). Data concerning the effect of salicylate upon the concentrations of these compounds in the blood have likewise been inconclusive (624, 854, 1468, 1601, 1781, 2132, 2527).

From present knowledge the effect of salicylate on nitrogen metabolism is limited mainly to the excretion of uric acid and although several explanations have been offered for this effect the omission of any of these explanations from most textbooks indicates the uncertainty concerning them.

Particular attention has been given to the excretion of uric acid probably because of the older beliefs concerning the association of this substance with rheumatism for which salicylates were prescribed. A marked increase in the excretion of uric acid in men following the administration of large amounts of salicylic acid and its salts has been repeatedly reported (358, 854, 856, 1079, 1317, 1442, 1525, 1578, 1601, 1732, 1781, 2401, 2462, 2737, 2832, 3093, 3094). Increased excretion of this metabolite has also been observed after administration of large amounts of acetylsalicylic acid (854, 930, 2944, 2945, 3241, 3246). A similar effect of salicylate on the excretion of uric acid has been reported in animals (2527, 3406, 3801). With small amounts of salicylate, however, an unaltered or even diminished excretion of uric acid has been observed in men by some investigators (1079, 2466, 2832, 3028).

Fauvel [1907] emphasized the importance of the amount of salicylate administered in relation to the effect on the elimination of uric acid, and Quick [1933] observed that an increased output of uric acid is stimulated only after a certain concentration of salicylate is attained in the body and ceases when the concentration falls below this level. He found that the level of salicylate which excites an increased uric acid excretion is higher than that necessary for analgesia but lower than that required in the treatment of rheumatic fever. Other investigators have attributed the extent of uric acid excretion to the cation moiety administered. Thus Suzuki [1931 (3406)] observed a decreasing effect of equivalent amounts of the potassium, calcium, magnesium, sodium and lithium salts of salicylic acid. Yamaguchi [1931] observed a marked increase in uric acid excretion in rabbits after administration of sodium bicarbonate with the salicylate, and a decrease with hydrochloric acid. Johnson and Hanzlik [1929] reported a much greater excretion of uric acid in men after ammonium salicylate than after sodium salicylate.

Goodbody [1900] and Jackson and Blackfan [1907] explained the increased excretion of uric acid following salicylate administration on the basis of an increased production of uric acid in the organism. Heck [1896] observed a leucocytosis in men following the administration of salicylate and attributed the increased uric acid excretion to the increased destruction of leucocytes. Other investigators, however, observed no leucocytosis under similar con-

coumarol has been administered; nor can any products be found in the urine which on fusion with potassium hydroxide result in salicylic acid. From the additional facts that dicoumarol possesses 25 to 100 times the prothrombinopenic action of salicylate, and that a small dose of vitamin K protects the rat against the hypoprothrombinemia from a large dose of salicylate, while a massive dose of vitamin K is required to counteract the effects of a small dose of dicoumarol, he concluded that there is no relationship between dicoumarol and salicylate in their prothrombinopenic actions.

The work of Link and his associates [1943] served to disclose the prothrombinopenic action of salicylate and numerous investigations have been reported on this action. From these reports it appears that salicylate does not inhibit the activity of prothrombin in plasma *in vitro* (685, 787, 2153, 3327a) but that salicylates in sufficient amounts can produce a hypoprothrombinemia in experimental animals (682, 685, 1104, 2153, 2858, 3198). Field [1945] has shown that the administration of 100 mg. of acetylsalicylic acid per kg. to lactating rats produces a hypoprothrombinemia in both the mothers and their suckling offspring. The intensity of the hypoprothrombinemia occurring in rabbits was found by Clausen and Jager [1946] to be correlated with the concentration of salicylate in the plasma.

Clark and Spitalny [1946] observed an interspecies difference in susceptibility to the prothrombinopenic effects of salicylate, the rat being markedly more sensitive than the rabbit, and the rabbit more sensitive than the dog. A similar observation was made by Rapoport, Wing and Guest [1943]. They found that the prothrombin time was unchanged in dogs receiving 0.6 cc. of methyl salicylate per kg., even though they were severely intoxicated. In rabbits given 0.5 cc. of methyl salicylate per kg., however, a severe hypoprothrombinemia developed in 48 hours. Overman and his associates [1944 (2649)] attributed this difference between species to the fact that a deficiency of vitamin K is produced with varying degrees of ease in the different species. Even in rats, Link and his associates [1943 (2153)] were able to induce a hypoprothrombinemia with a single dose of sodium salicylate only in animals maintained on a ration low in vitamin K. Repeated administrations of salicylate, however, caused a hypoprothrombinemia even when the stock ration contained an adequate supply of vitamin K.

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HYPOPROTHROMBINEMIC ACTION OF SALICYLATES AND ITS
RELATION TO HEMORRHAGE

A possible relationship between intensive salicylate medication and bleeding has been repeatedly suggested in the literature. In 1884 Balette stated that sodium salicylate might cause menorrhagia, prolonged menstrual periods, hematuria, epistaxis or hemorrhages in the intestines. Fischer [1905] was convinced that the marked epistaxis he observed in a girl receiving daily doses of 4 to 5 g. of acetylsalicylic acid was caused by the drug. Link [1944] referred to the observations of Binz [1893], Wetzel and Nourse [1926], Balázs [1930], Madisson [1934] and Hurst and Lintott [1939] in pointing out that hemorrhage often occurs in individuals receiving large doses of salicylates.

A possible explanation for this bleeding has been suggested. It was derived from studies made on dicoumarol. When cattle feed on spoiled sweet clover hay they may develop a hemorrhagic disease which, as Stahmann, Huebner and Link* have shown, is caused by 3,3'-methylene-bis[4-hydroxycoumarin], dicoumarol. In determining the structure of this compound, they found that on fusion with potassium hydroxide it was quantitatively converted into salicylic acid.

Link and his associates [1943 (2153)] then offered the theory that dicoumarol is metabolized to salicylate in the body and that this metabolite causes a hypoprothrombinemia which results in hemorrhage. They demonstrated that salicylate may cause hypoprothrombinemia.

Subsequent observations of other investigators, however, have indicated that the decrease of prothrombin in the plasma caused by dicoumarol is quite distinct from that caused by salicylates. Although Link and his associates were impressed with the fact that all of the compounds investigated by them which produced a hypoprothrombinemia could be degraded to salicylic acid, Kabat, Stohlmann and Smith [1944] have shown that 2-pivalyl indandione and other indandione derivatives have a prothrombinopenic action equal to that of dicoumarol but would be expected to be metabolized to phthalic acid and not salicylic acid in the body. Lester [1944] found that no salicylate can be detected in the urine of rats to which di-

*Stahmann, M. A., Huebner, C. F. and Link, K. P. J. *biol. Chem.* 138: 513, 1941.

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salicylate and methyl salicylate to have approximately the same prothrombinopenic activity in rats. In rabbits, methyl salicylate was less active. The same investigators reported that the hyperthermia induced in rats with yeast injections or by exposure to a high environmental temperature has a hypoprothrombinemic effect which is synergistic with that of salicylate. Even if the salicylate is given before the yeast, so as to prevent fever, the hypoprothrombinemic effect of the salicylate is enhanced.

A prothrombinopenic effect of salicylate in man has been reported in the past few years by many investigators (521, 685, 729, 1075, 2036, 2153, 2353, 2424, 2538, 2539, 2651, 2858, 3195, 3198, 3633). In most of these reports the doses of salicylate were high and administration was continued for several days.

Some of these investigators reported that there was no relationship between the concentration of salicylate in the plasma and the degree of hypoprothrombinemia (1075, 2651); others (685, 729) observed a correlation up to a concentration of salicylate in the plasma of 70 mg. per 100 cc. A possible explanation of this discrepancy may be found in the observation reported by several investigators (521, 1075, 2651) that in long-continued salicylate medication there is an initial hypoprothrombinemia which then diminishes although salicylate administration is continued. Any relationship between the concentration of salicylate in the plasma and the prothrombinopenic effect may depend on the period of time over which salicylate had been given.

Single administrations of salicylate and repeated administration of small amounts were reported by some investigators to have no prothrombinopenic effect. Thus Meyer and Howard [1943] observed no effect from single doses of 30 to 40 gr. of acetylsalicylic acid, although 20 gr. daily for 7 days resulted in hypoprothrombinemia. Di Cio and Bay [1944] found no significant decrease in prothrombin when 2.8 g. of a mixture of salipyrine, sodium salicylate and acetylsalicylic acid was given daily for 12 days to 39 patients with peripheral arteriopathy. Lester* found no hypoprothrombinemia in 5 normal subjects receiving 30 gr. of acetylsalicylic acid daily for 11 days. Coombs, Higley and Warren [1945 (729)] observed no significant prothrombin change in 15 nonrheumatic patients given 1, 2, 3 and 6 g. of sodium salicylate daily. Although,

*Personal communication.

in measuring the prothrombin time, differently prepared thromboplastin and various dilutions of plasma were used, and with some effect on results, it was generally found that small doses of salicylate had no clinically significant thrombopenic effect.

Vitamin K or K-like compounds have been found to be effective in man in the treatment of hypoprothrombinemia caused by salicylate medication (2424, 2538, 2539). Shapiro [1944 (3195)] has reported that 1 mg. of synthetic vitamin K given intravenously prevented the hypoprothrombinemia caused by the daily administration of 1 g. of acetylsalicylic acid. Clausen and Jager [1946] did not find it to be effective in patients with acute rheumatic fever or active rheumatoid arthritis; moderately large doses of vitamin K given to these patients during salicylate therapy did not prevent hypoprothrombinemia. Shapiro, Redish and Campbell [1943 (3198)] found that vitamin K completely prevented the hypoprothrombinemia in healthy men but not in a patient with liver cirrhosis and they have suggested that the finding of Clausen and Jager may be due to the disease process in their patients. Fashena and Walker [1944] reported that synthetic vitamin K only partially controlled the hypoprothrombinemia in a 9-year-old boy with acute rheumatic fever.

A relationship between prothrombin time and clotting time has been shown by several investigators. Fashena and Walker [1944], after giving 70 g. of sodium salicylate to a patient during a 2-week period, observed a prothrombin time of $2\frac{3}{4}$ minutes, a bleeding time of $5\frac{1}{2}$ minutes and a clotting time of 10 minutes; the ingestion of 4 mg. of synthetic vitamin K reduced these respective times in 1 day to $1\frac{1}{4}$, $2\frac{1}{2}$ and 4 minutes; on the following day they were 45 seconds, $1\frac{1}{2}$ and 2 minutes. Meyer and Howard [1943] found that the coagulation time of whole blood is prolonged whenever there is an increase in the prothrombin time and Fashena and Walker [1944] made further observations supporting the relation between bleeding and clotting times and hypoprothrombinemia.

There has been less agreement concerning the relation between hypoprothrombinemia and hemorrhage following salicylate administration. In 1 patient Fashena and Walker [1944] reported no hemorrhage, although hypoprothrombinemia occurred. In 399 patients with rheumatic fever treated with massive doses of salicylate Coombs, Higley and Warren [1945], Warren, Higley and Coombs [1945 (3633)] and Butt and his associates [1945] found no

hemorrhagic manifestations. In a smaller group of patients with rheumatic fever receiving similar salicylate therapy Owen and Bradford [1946] reported 5 cases of epistaxis, in 2 of which there were also splinter hemorrhages under the fingernails. In these 5 cases the prothrombin of the plasma was diminished more than 72 per cent. Because of the transient character of the hemorrhage as compared with the protracted hypoprothrombinemia, the investigators did not believe that the hypoprothrombinemia and the hemorrhage were causally related.

The absence of post-tonsillectomy hemorrhage, observed in European countries, was attributed by Singer [1945] to the fact that salicylate was not used there in postoperative therapy. In a group of 75 tonsillectomies performed without the administration of salicylate no hemorrhage was observed. Neivert [1945, 1946] found a 10-per-cent incidence of hemorrhagic inflammation of the soft palate and secondary hemorrhage after tonsillectomy in patients given salicylate; in a group of 173 post-tonsillectomy patients treated with acetylsalicylic acid and vitamin K, the incidence was only 1.4 per cent. However, Neivert, like Owen and Bradford [1946], concluded that the hypoprothrombinemia is not alone responsible for the bleeding.

In a later chapter dealing with poisoning by salicylates, clinical and post-mortem data are presented indicating that hemorrhage occurred in about one-fifth of nonallergic cases of poisoning. The bleeding occurred in brain meninges and dura, in pericardium and endocardium and sometimes in myocardium, in pleurae and occasionally in the lungs, kidneys, spleen, skin, gastric and intestinal mucosa and, rarely, in muscle. In a great number of these cases it was especially noted that hemorrhages were petechial or ecchymotic.

There is little doubt, from present knowledge, that salicylate in sufficiently large dosage exercises a prothrombinopenic effect in man, and that hypoprothrombinemia is associated with a prolonged bleeding and clotting time. It is further suggested, from the literature, that this effect, although not the only cause, may be a contributing factor in the hemorrhages observed in diseases for which salicylate has been given in large and repeated doses. The prothrombinopenic effect of salicylate is limited to large doses, repeatedly administered over a prolonged period of time, and there is no evidence that small doses of salicylate as used for analgesic effects cause any clinically significant hypoprothrombinemia.

INFLUENCE ON ERYTHROCYTE SEDIMENTATION RATE

It has long been known that a high erythrocyte sedimentation rate is a characteristic symptom of acute rheumatic fever. In the successful treatment of this disease with salicylate, a prompt fall in the sedimentation rate has frequently been observed (201, 696, 753, 1849, 2036, 2244, 2329, 3437, 3577, 3633, 3634, 3655), suggesting that salicylate decreases the sedimentation rate by arresting the activity of the disease which caused its increase.

Some investigators have attributed the diminishing of the erythrocyte sedimentation rate by salicylate to a direct action of the drug on the plasma, and therefore independent of any therapeutic effectiveness. Bendien, Neuberg and Snapper [1932] reported that sodium salicylate added to blood *in vitro* decreased the sedimentation rate. They attributed this effect to an increased stability of the colloidal state of the plasma proteins. In patients with rheumatic fever who, under salicylate treatment, recovered and attained a normal sedimentation rate Lichty and Hooker [1941] observed an increase in the sedimentation rate immediately on cessation of administration of salicylate. The rapidity of this increase suggested to these observers that salicylate reduces the sedimentation rate directly rather than by reducing the activity of the rheumatic fever. This suggestion finds support in observations first reported by Bendien, Neuberg and Snapper [1932] that salicylate reduces the sedimentation rate when added to blood *in vitro*, although the concentration of salicylate necessary for this was two to three times that required for adequate therapy.

Homburger [1945] also observed a decrease in the sedimentation rate of blood from rheumatic patients on the addition of salicylate *in vitro*. He attributed this action, as did Bendien, Neuberg and Snapper, to the effect of salicylate on the stability of the plasma proteins. A similar explanation was suggested by the observations of Coburn and Kapp [1943] of the action of salicylate on certain antigens and immune bodies in plasma.

A third explanation offered for the effect of salicylate on the sedimentation rate of erythrocytes was that the drug, through its action on the liver, alters the fibrinogen content of the plasma and thus affects the sedimentation rate. In treating patients having rheumatic fever or other diseases with salicylate, Rapoport and Guest [1946] found a decrease in the concentration of plasma

fibrinogen as well as in the sedimentation rate. Homburger [1946 (1655)] observed similar effects of salicylate on sedimentation rate and plasma fibrinogen in three patients' with carcinoma. Salicylate added to plasma from these patients *in vitro* resulted in no change in the concentration of fibrinogen. Homburger concluded that the decrease in the sedimentation rate *in vitro* is due to both the direct action of the salicylate on the plasma and to the action of the drug on liver function in altering the fibrinogen content of the plasma. There is no proof or preponderance of evidence for one or another of the explanations offered for the effect of salicylate on the sedimentation rate of erythrocytes in rheumatic fever. That salicylate therapy, however, yields favorable results in rheumatic fever and that a decrease in the sedimentation rate under this therapy is a good indication of arrested activity of the disease is common clinical knowledge.

INFLUENCE ON EXCRETION OF ASCORBIC ACID

The possibility of vitamin C deficiency arising from the prolonged administration of salicylates was first suggested by the work of Daniels and Everson [1936] who reported that the administration of acetylsalicylic acid to three children was followed by an increased elimination of ascorbic acid in the urine. The extensive use of salicylate in the therapy of rheumatic fever makes the question of an effect on the elimination of vitamin C an important one. The investigations reported in the literature have been contradictory. This contradiction, and indeed the whole matter of excretion of ascorbic acid as reported upon, may be influenced in part by the analytical method employed for determining ascorbic acid in the urine.

In all investigations in which an increased excretion is reported the concentration of ascorbic acid was determined by direct titration with 2,6-dichloroindophenol. It has recently been shown that vitamin C may be excreted either as the reduced ascorbic acid or the reversibly oxidized dehydroascorbic acid. The latter is biologically active but is not measured by direct titration. The only investigation of the effects of salicylate on the vitamin C in the body in which total vitamin C was determined was that of Richeri and Litter [1939]. They found no significant change in the vitamin C content of the blood of rheumatic and normal human beings given large daily doses of sodium salicylate.

The results of all other investigations to be reported here must be viewed in the light of possible inadequacy in the analytical methods used and definite conclusions concerning the effect of salicylate on vitamin C excretion must await the results of further studies.

The findings of Daniels and Everson [1936] as to the increased elimination of ascorbic acid after administration of acetylsalicylic acid were confirmed by Keith and Hickmans [1938] in children with rheumatic fever under treatment with salicylate. Youmans and his associates [1937] and van Eekelen [1937] were unable to find an increased elimination in healthy adults given salicylate. Richeri and Litter [1939], as stated above, using more adequate analytical methods, could not find any change in the vitamin C content of the blood of rheumatic and normal subjects given large amounts of sodium salicylate daily.

Longenecker and his associates [1939] concluded that acetylsalicylic acid stimulates the synthesis of vitamin C in rats and that the increase results in a larger excretion. Samuels, Ritz and Poyet [1940] observed an increased excretion of ascorbic acid in rats and guinea pigs given sodium salicylate or acetylsalicylic acid orally, but found that if the guinea pigs were maintained on a vitamin-C poor diet only a slight increase in excretion occurred. Lutwak-Mann [1942, 1943] also observed in the urine of rats after the administration of salicylate an increase in reducing substance which was presumed to be ascorbic acid.

Ritz, Samuels and Adiss [1940] studied the effect of sodium salicylate and acetylsalicylic acid on the concentration of ascorbic acid in organs, blood plasma and urine of rats. They reported that 300 mg. of the salicylate per kg. given twice daily increased the urinary excretion of ascorbic acid and decreased its content in the brain and, to a lesser extent, in the liver and other organs. The concentration of ascorbic acid in the blood plasma was not significantly affected. In nephrectomized rats, however, the salicylate caused an increased concentration of ascorbic acid in the blood plasma and a lowered concentration in the brain. Longenecker, Fricke and King [1940] observed an increased excretion of ascorbic acid in rats given salicylate.

And finally Pelner [1942] suggested that ascorbic acid is in some way bound with salicylate. A few crystals of ascorbic acid discolored a diluted solution of methylene blue on heating; if the

methylen blue solution contained some sodium salicylate, however, no discoloration occurred.

ANTISEPTIC ACTION

The inhibiting action of salicylate on the growth of microorganisms was first observed by Kolbe [1874]. His primary interest was in the synthesis of salicylic acid but in the course of his work he noted that this drug prevented the fermentation of sugar and beer, retarded the coagulation of milk, preserved meat and eggs, and inhibited the decomposition of urine. The growth-inhibiting power of salicylic acid on microorganisms led Thiersch [1875] to use the compound as an antiseptic in the treatment of wounds. Since then reports have frequently appeared in the literature concerning the antiseptic properties of the salicylates and their effect on various organisms.*

Recently the United States Department of Agriculture reported [Clayton (688)] that bismuth subsalicylate, salicylic acid and zinc salicylate are effective against blue mold, a tobacco disease. Findlay [1943] found that acetylsalicylic acid inactivates the neurotropic strain of yellow fever virus.

Ivánovics [1942, 1943] attributed the antiseptic action of salicylate to an inhibition of the synthesis of pantothenic acid by the microorganisms. There was no antiseptic effect of salicylate with organisms requiring no pantothenic acid for growth. Stansly and Schlosser [1945] and Stansly and Alverson [1946] confirmed Ivánovics' observations.

Küster and Wagner-Jauregg [1944] found that low concentrations of sodium salicylate retarded the growth of tubercle bacilli. Lehmann [1946] reported a similar effect of p-aminosalicylic acid, also in low concentrations, and in 20 patients with tuberculosis treated with this drug he reported temporary or permanent improvement.

EFFECT ON BACTERIAL TOXINS

The ability of salicylate to detoxify tetanus toxin *in vitro* was observed by Vincent in 1928. By means of dialysis Vincent [1931 (3582)] found that the salicylate ion becomes bound to the toxin, and in the immunization of rabbits by the repeated administration

*For reference list see p. 131.

of tetanus toxin the injurious effects of the toxin were markedly diminished by the simultaneous administration of salicylate (3581).

Velluz [1932] observed that 40 to 50 mg. of sodium salicylate neutralized the toxicity of 500 times the lethal dose of tetanus toxin in 4 to 5 days, and that salicylic acid was more effective, 25 mg. neutralizing 500 times the lethal dose of toxin in 6 hours, and 5 mg. in 4 days.

Birkhaug [1931] found that saturated solution of sodium salicylate completely neutralizes the toxicity of tetanus and diphtheria toxins without destroying their ability to produce antibodies. The extent of neutralization of toxicity is dependent on the concentration of salicylate, the duration of contact, and the temperature. This investigator did not explain the reason for this action of salicylate on the toxins but suggested that the effect together with the antiseptic action of salicylate is responsible for the successful therapeutic use of the drug in certain infectious diseases. No diminution of toxicity was exercised by salicylate on the toxins of hemolytic and nonhemolytic streptococci.

EFFECT ON ENZYME ACTION

In 1874 Müller observed that, *in vitro*, 1 per cent salicylic acid inhibits the action of ptyalin, and that 0.1 per cent retards and 0.5 per cent completely inhibits the conversion of liver glycogen to glucose. He also found that the digestive action of pepsin was retarded by 0.2 per cent salicylic acid and delayed even by 0.05 per cent (2496).

Heusch [1912] reported that low concentrations of salicylic acid increased the action of malt diastase on starch but larger concentrations inhibited the action. Succindehydrogenase was found to be markedly inhibited by sodium salicylate (2575) and saccharase only slightly (1046).

Lutwak-Mann [1942] studied the effect of salicylate on the action of various animal, plant and yeast enzymes and found that the activity of xanthine oxidase, carboxylase, indophenol oxidase, and certain dehydrogenases was inhibited by salicylate; glucose fermentation by yeast and dismutation between hexosediphosphate and pyruvate were also inhibited. An inhibiting effect of salicylates was also reported by other investigators on the action of lactic acid dehydrogenase (1045), glucose-lactose dehydrogenase (15), and cholinesterase (811).

Guerra [1946] reported recently that sodium salicylate inhibits the enzymatic action of hyaluronidase on the hydrolysis of hyaluronic acid in the body and thus diminishes the diffusion or spread of materials in the body. The importance recently attached to hyaluronidase and spreading factors in infection (2422a) suggests a particular significance of sodium salicylate as an antirheumatic drug.

EFFECT ON SKIN AND MUCOUS MEMBRANE

The different salicylate compounds show marked differences in their irritating properties; some cause little irritation while others, especially salicylic acid itself, are not only irritating to the skin and mucous membrane but they have a strong keratolytic action and are used therapeutically for this purpose. Hodara [1896] first observed that salicylic acid produces swelling of the horny layer with exfoliation and formation of scales; edema of the granular and prickle cells results, and it may be followed by a greatly increased activity of the germinal layer resulting in rapid regeneration.

Manasse [1900 (2291)] compared the effect of acetylsalicylic acid and salicylic acid on the skin. Three grams of each of these substances were applied to an arm with an airtight bandage for 3 days; with salicylic acid the result was a severe erythema resulting; but with acetylsalicylic acid no such hyperemia occurred. An irritating action of both compounds on the tails of fish was observed by Dreser [1907].

The external application of liberal amounts of some salicylate esters (monoglycol salicylate, o-hydroxybenzylalcohol) but not methyl salicylate was found by Sauerland [1912 (3038)] to cause dermatitis in human subjects. The salts of salicylic acid, even in high concentrations, were reported to be nonirritating by Hanzlik [1927].

Methyl salicylate as well as other salicylate esters, when applied liberally, causes rubefaction, and for this reason, as will be shown later, has been widely used as a counterirritant.

LOCAL EFFECT ON BLOOD VESSELS

The occluding action of salicylate on blood vessels was first investigated by Binet and Verne [1925]. After intravenous injections of a 30-per-cent solution of sodium salicylate in rabbits they ob-

served that endophlebitis developed and clots were found. Meisen [1926] made microscopic studies of the blood vessels of horses injected intravenously with a 40-per-cent solution of sodium salicylate. He found an intense inflammatory reaction in the adventitia and hemorrhagic edema in the perivascular tissue. The thrombi which formed nearly filled the lumen of the vessels; they became organized in 2 to 14 days.

Kilbourne, Dodson and Zeiler [1932] reported that a 30-per-cent solution of lithium salicylate in 0.75 per cent tutocaine injected into rabbits produced sloughing equal to that caused by a sodium salicylate solution of the same strength.

In dogs, Kern and Angle [1929] examined the veins after intravenous injection of a 20-per-cent sodium salicylate solution. On the second day following injection they found a decrease in diameter due to collapse and thickening of the vessel walls. Thrombi were formed which were not easily dislodged. None of the animals died of embolism or showed signs of pulmonary infarction.

Ochsner and Garside [1932] made a detailed study of the histological changes in blood vessels of dogs after intravenous injection of various concentrations of sodium salicylate dissolved in water and in sugar solutions. Sections of the vessels were removed at intervals after injection and the changes occurring in the endothelium, media and adventitia were studied microscopically. In the endothelium they found vacuolization, pyknosis and destruction of the cells; in the media, edema, leukocyte infiltration, hemorrhage, fibrosis and destruction; and in the adventitia, dilatation of the vasa vasorum and fibrous thrombi.

EFFECT ON GROWTH

Kaiser [1936] gave 10 to 15 gr. of acetylsalicylic acid with magnesium oxide daily to 75 children for periods of 6 months to 1 year. No effect was observed on the rate of increase in weight and height as compared to 75 control children.

Krantz, Iwamoto and Farson [1946] fed a basic diet with 0.5 per cent acetylsalicylic acid or 0.2 to 0.5 per cent acetyl-5-bromosalicylic acid to rats for 8 weeks and measured their growth. In the animals given the acetylsalicylic acid there was no retardation of growth, while in those receiving acetyl-5-bromosalicylic acid there was virtually no growth.

LETHAL DOSAGE OF SALICYLATES

Numerous observations have been made with a variety of salicylates on the amount of salicylate required to cause death in various species of animals and under various modes of administration. In experiments where a sufficient number of animals were tested, both minimum lethal doses and the doses at which half the animals died (LD 50) have been determined.

Alkali salicylates. In frogs 50 mg. of sodium salicylate was found by Dreser [1907] to be fatal. Waddell [1911] determined the lethal dosage of sodium salicylate, given hypodermically, in cats, rats and rabbits, with the findings shown in Table 11. It will be seen that rabbits appear to be less sensitive to the drug than rats and cats. The range of lethal dosage for rats was 500 to 1,400 mg. per kg.; for cats, 800 to 1,400 mg. per kg. (none was given less than 800 mg. per kg. and this was fatal); and for rabbits, 1,000 to 1,600 mg. per kg.

TABLE 11.—*Lethal Doses of Sodium Salicylate for Cats, Rats and Rabbits. Subcutaneous Administration**

Dose (mg./kg.)	CATS		RATS		RABBITS	
	No. of Animals	No. of Deaths	No. of Animals	No. of Deaths	No. of Animals	No. of Deaths
350			8	0		
500			5	1		
650			8	7		
750			6	6		
800	1	1				
900	2	2				
1,000	4	4	2	2	4	1
1,100	2	2				
1,140					8	5
1,200	5	5			7	3
1,300						
1,400	3	3	6	6	4	1
1,600					3	3

*Data of Waddell (3607).

The lethal dosage of sodium salicylate in frogs was determined by von Issekutz [1913] as 1.2 mg. per g. of body weight. Bartholow and McNeil [1917] found in rabbits no difference between the toxicity of natural and synthetic sodium salicylate; about 800 mg. per kg. intravenously and approximately 2,600 mg. per kg. orally were fatal.

In 8 cats, Laqueur and Magnus [1921] found that sodium salicylate given subcutaneously was fatal in doses in excess of 150 mg. per kg. This value for the lethal dose of sodium salicylate is so low, compared to those obtained by all other investigators and for any route of administration, that its validity is questionable. The minimal lethal dose of sodium salicylate for mice was determined as approximately 600 mg. per kg. by Winter and Barbour [1928].

Johnson and Hanzlik [1929] determined the minimum fatal dose of ammonium salicylate given hypodermically as approximately 600 mg. per kg. for rats and as 550 mg. per kg. for mice.

Kilbourne, Dodson and Zeiler [1932] gave sodium salicylate to rabbits intravenously and found that after 600 mg. per kg. three animals died and three did not. Madisson [1934] found that given intravenously 300 to 400 mg. of sodium salicylate per kg. was generally fatal to rabbits, although some animals survived 500 and 600 mg. per kg. With oral administration one rabbit died after 700 mg. per kg., another survived 1,100 mg. per kg. The younger and smaller animals showed a higher resistance to fatal poisoning than the older and larger ones.

McGuigan and Higgins [1935] gave repeated intravenous injections of sodium salicylate to 2 dogs. One dog died after 470 mg. per kg., the other after 600 mg. per kg. Delphaut [1936 (838)] also gave dogs sodium salicylate by slow intravenous injection and reported that the lethal dose in 10 dogs varied from 900 to 1,540 mg. per kg.

Eichler and Bengelforth [1938] reported that for rats 1 g. of sodium salicylate per kg. given orally was not fatal; after 1.5 and 2 g. per kg. half the animals died; after 2.5 g. per kg. 13 of 15 animals died. Administration of sugar did not diminish the toxicity of sodium salicylate, and sugar with insulin increased it.

Torino and Litter [1941] gave synthetic sodium salicylate and the "natural" product intravenously in various doses to 180 mice. No significant difference was found between the toxicity of the two. The percentages of deaths occurring at various doses are shown in Table 12. The lethal dose ranged between 400 and 800 mg. per kg.

Acetylsalicylic acid. In 1899 Dreser (930) reported that 63 mg. of sodium acetylsalicylate killed a frog in about $7\frac{1}{2}$ hours. Barbour and Lozinsky [1923] administered 1 g. of acetylsalicylic acid per kg. subcutaneously to 2 rats; 1 died and the other survived; 2, 4

and 8 g. per kg. killed all of the rats. Ruddiman and Lanwermyer [1924] found the minimum lethal dose of acetylsalicylic acid in frogs to be approximately 0.4 mg. per g. The lethal dose of acetylsalicylic acid by intravenous administration in rabbits was given as 700 mg. per kg. by Simon [1933]. The toxicity of orally given acetylsalicylate was determined in 50 rabbits by Climenko [1936]. His findings are shown in Table 13 where it will be seen that the lethal dose was between 750 and 2,000 mg. per kg. The simultaneous administration of magnesium oxide had no marked influence on the toxicity.

Brownlee [1937] determined the toxicity of orally administered acetylsalicylic acid in 36 mice. At a dose of 750 mg. per kg. no animals died; at a dose of 1,750 mg. per kg. all died. From the percentage of fatalities at various doses between these two values the LD 50 was calculated to be 1,360 mg. per kg. A similar procedure was carried out using rats (461). At a dose of 500 mg. per kg. no rats died; at 1,750 mg. per kg., all died. The LD 50 was calculated to be 1,240 mg. per kg.

TABLE 12.—*Lethal Doses of Sodium Salicylate for Mice.*
*Intravenous Administration**

<i>Dose</i> (mg./kg.)	SYNTHETIC SODIUM SALICYLATE		NATURAL SODIUM SALICYLATE	
	<i>No. of</i> <i>Animals</i>	<i>Per Cent</i> <i>Deaths</i>	<i>No. of</i> <i>Animals</i>	<i>Per Cent</i> <i>Deaths</i>
200	30	0.0	30	0.0
400	30	10.0	30	3.3
600	30	83.3	30	83.3
800	30	100.0	30	100.0
1,000	30	100.0	30	100.0

*Data of Torino and Litter (3507).

TABLE 13.—*Lethal Dose of Acetylsalicylic Acid for Rabbits.*
*Oral Administration**

<i>Dose (mg./kg.)</i>	<i>No. of Animals</i>	<i>Per Cent Deaths</i>
200	5	0
400	5	0
750	5	20
1,000	10	50
1,200	5	40
1,500	10	80
2,000	10	100

*Data of Climenko (692).

Methyl salicylate. Chatin and Guinard [1900 (645)] gave methyl salicylate to dogs and rabbits. They found that 2 cc. given subcutaneously produced no effect; 3 cc. given intravenously killed a dog in 5 minutes; and 3 cc. or more given intraperitoneally killed rabbits. According to Houghton [1905] the minimum lethal dose of methyl salicylate given orally to guinea pigs is 700 mg. per kg.

Salicylic acid. Hildebrandt [1904] reported that injection of 9 to 13 mg. of salicylic acid was fatal to mice and Stockman [1913] that 4 to 6 g. of salicylic acid, given orally, was fatal to rabbits.

Calcium acetylsalicylate. Thompson and Dragstedt [1933] determined the lethal dose of calcium acetylsalicylate given intravenously to dogs as 600 to 750 mg. per kg. According to Stutzman, Orth and Mellish [1941] the minimum lethal oral dose of this compound in rats is about 1,200 mg. per kg.; 15 rabbits given 1,200 mg. per kg. orally survived.

Salicylsalicylic acid. Tocco [1912] reported that rabbits were killed by oral doses of 3 g. per kg. of this drug; dogs, by 1.3 to 1.4 g. per kg.

Strontium acetylsalicylate. Simon [1934 (3242)] found that rabbits survived oral administration of 1.17 g. of this compound per kg. but that 1.3, 1.4 and 1.5 g. per kg. were fatal.

Antipyrine salicylate. Hale [1909] found that in mice the minimum lethal dose of antipyrine salicylate, given subcutaneously, was between 1,100 and 1,200 mg. per kg.

Salicyluric acid. Hanzlik and Seidenfeld [1930] determined the minimum lethal dose of this compound, given subcutaneously and intravenously, as approximately 1.13 g. per kg. for mice and 3.0 g. per kg. for rats.

Ethyl salicylate. According to Houghton [1905] the minimum fatal dose of this compound for guinea pigs is 1,400 mg. per kg. given subcutaneously and 1,500 mg. per kg. given orally.

Amyl salicylate. Chanoz and Doyon [1900 (630)] reported that 500 to 800 mg. of amyl salicylate per kg., given intravenously, was fatal to rabbits and dogs in a few minutes.

Lethal Dose of Salicylate for Man

The lethal dose of salicylate for man is largely a matter of opinion based on unavoidably unreliable evidence. Few instances of fatal poisoning have occurred when the administration was reliably observed by a physician and the exact dose known. In most instances

the dose is approximated by circumstantial evidence such as an empty bottle marked as originally containing some amount of salicylate or, more often, the word of the family that the victim took 15 or 20 tablets during the day. Such evidence has little quantitative validity as compared to precise experimental studies on animals. Nevertheless the literature often gives it such a validity, particularly when, as in textbooks, only a summary statement is made and the qualifying details of the original report are omitted. It is in part because of this fact that the lethal dose of salicylate for man shows a vastly wider range than for animals.

A second point of uncertainty lies in the designation of the cause of death as due to salicylate. In many instances, as when an individual is acutely ill and dies following a seemingly small dose of salicylate, the decision as to whether the salicylate was the main cause or a contributing cause or of no cause in the fatality is wholly a matter of opinion. The uncertainty as to the lethal dose is reflected in the amounts cited, particularly, in textbooks on toxicology. Thus Kobert [1906] expressed the opinion that 3 g. of salicylic acid might be fatal; Peterson, Haines and Webster [1923] and McNally [1937] emphasize their uncertainty with the statement that the lethal doses reported for man show wide variation. McNally states, however, that acetylsalicylic acid is about half as toxic as sodium salicylate but that he has never seen a fatality from overdose of acetylsalicylic acid. Caussade and Charpy [1921] give the lethal dose of salicylic acid as 10 to 12 g. Goodman and Gilman [1941] express the opinion that the lethal dose of sodium salicylate is between 10 and 30 g. but note that there have been survivals after larger doses.

On the basis of animal experiments Wokes [1938] estimated the lethal dose of acetylsalicylic acid as 10 to 30 g., but as Hamill [1939] has pointed out, men have survived after doses of 26 to 33 g. Eichholtz [1939] estimated the lethal dose of acetylsalicylic acid to be 30 to 40 g. and Thienes [1940] gives the acutely fatal dose of salicylate for adults as about 30 g.

Based on opinions expressed in the literature the lethal dose of salicylate ranges from 3 to 12 g.; of sodium salicylate from 10 to 30 g.; and of acetylsalicylic acid, 10 to 30 g. or higher.

In a later chapter of the present review all of the alleged lethal poisonings by salicylate reported in the literature, 136 in number, are described. (In addition there were 8 deaths in individuals allergic

to acetylsalicylic acid, which are dealt with separately.) In only 72 of these cases was the poisoning acute, i.e., the salicylate was taken during a period not exceeding 24 hours. Many of the individuals in this group were severely ill with some disease; many others took salicylate for the purpose of suicide. The allegations of those with self-destructive intentions concerning the amount of drug taken must be considered with doubt. A similar doubt applies to the statements of members of the families of those who have taken an overdose in self-medication or by accident. The acutely lethal dose of salicylate in normal or reasonably healthy human beings is, as indicated by the statements in the textbooks on toxicology mentioned, difficult to estimate from the available clinical data.

The smallest amounts of sodium salicylate reported to have caused death were 4 g. in an individual with rheumatic fever and 5 g. in a patient with typhoid. In an adolescent patient with rheumatic fever 25 g. of sodium salicylate was fatal and in two adults, the same dose. That 4 or 5 g. of sodium salicylate given to an adult should be lethal seems unusual in view of the fact that several times these amounts are frequently administered daily for long periods, in the treatment of rheumatic fever, without fatality.

The smallest amount of acetylsalicylic acid alleged to have caused death was 1.3 g. Friedman [1938] reported on a patient who had an acute illness starting with headache, vomiting and chills. He was presumed to have taken this amount of acetylsalicylic acid and died 3 days later. Although Friedman did not consider the symptoms characteristic of salicylate poisoning and was also doubtful as to the amount of salicylate consumed by the patient, the diagnosis was recorded as one of acetylsalicylic acid poisoning. Since acetylsalicylic acid was found in the tissues on necropsy 3 days after taking the salicylate, there is no doubt that this patient took salicylate and probably in larger or repeated doses.

Other than this case* the smallest doses of acetylsalicylic acid

*During publication of this review two additional instances of fatal poisoning from acetylsalicylic acid were reported by Krasnoff and Bernstein [1947]. In one, an adult who had been given acetylsalicylic acid for headache had increased the amount, according to the statements of his family, to "fifteen to twenty 5 grain tablets." He died some 20 hours later with symptoms and autopsy findings typical of salicylate poisoning. In this case, which was intensively studied, a determination for "aspirin" was made in the stomach contents and blood. Unfortunately, no numerical value was reported for the concentration found, which was simply

reported as fatal were 20 and 21 g. in three individuals (1757). There are records of two individuals who survived 80 g. of acetylsalicylic acid (1662, 2977), and of one who survived 97 g. (1047).

The smallest dose of methyl salicylate reported as fatal to adults was 4.8 cc. (1997). Of two individuals who each drank 6 cc. of this drug, one survived (1670). In children under 3 years of age the smallest fatal doses of methyl salicylate reported are 4 to 7 cc. (1011, 1685, 1823, 2804, 3342).*

One fatality has been reported from a single dose of 8 g. of phenyl salicylate (1977).

ADDITIONAL REFERENCES

Analgesic Action:

822, 1583, 1931, 2769, 2771, 3694, 3779.

Antipyretic Action:

181, 284, 305, 367, 403, 425, 680, 826, 1059, 1219, 1270, 1616, 1865, 2246, 2421, 2723, 3020, 3489, 3779, 3802.

Cardiovascular System:

20, 286, 512, 819, 1099, 1720, 1721, 1722, 1762, 1989, 2056, 2364, 2517, 2570, 2615.

Respiratory System:

158, 162, 295, 329, 1143, 2019, 2613, 3332.

Gastrointestinal System:

316, 329, 359, 395, 512, 796, 1447, 1668, 1695, 2273, 2723, 3289, 3467, 3632, 3691, 3865, 3901, 3935, 3981.

stated as a "high concentration of 'aspirin.'" It is regrettable that a quantitative value was not given since it would have yielded much better evidence as to dosage than the questionable evidence from the statements of the family upon which the validity of the report rests. The second instance was that of a child, age 5 months, said to have been given 2 g. of acetylsalicylic acid in a period of 10 hours before admission to a hospital.

*Two additional instances of poisoning from methyl salicylate, one fatal, were reported by Cancelmo [1947] during publication of the present review. In one, an adult male drank an estimated 90 cc. of oil of wintergreen. About $\frac{1}{2}$ hour later he became excited and irrational and shortly thereafter he lapsed into unconsciousness. He was admitted to a hospital $1\frac{1}{2}$ hours later and died 3 hours after taking the drug. Prior to death large quantities of material reeking of oil of wintergreen were aspirated from the stomach. On autopsy, the odor of oil of wintergreen emanated from the entire bowel.

In the second case an adult male drank about 30 cc. of oil of wintergreen. One-half hour later he became weak and dizzy and complained of generalized abdominal pain. He was admitted to a hospital. About 1 hour later he became comatose. His course thereafter was stormy and he remained in coma for some 12 hours. His condition then began to improve and blood drawn at this time had a salicylate concentration of 125 mg per 100 cc. His recovery was rapid and uneventful.

Therapeutic Uses

THE production of acetylsalicylic acid in the United States in recent years has been greater than that of any other medicinal drug intended mainly for internal use; the production of salicylic acid was second largest. The amounts of various salicylate compounds produced during the period 1941-44, as reported by the United States Tariff Commission, are shown in Table 14.

RHEUMATIC FEVER

The use of salicylate in the treatment of rheumatic fever was first reported on in 1876 and since then more than 300 papers have been published dealing primarily with this therapy of the acute disease. In virtually all there is agreement as to the relief of pain and inflammation of the joints but there is considerable disagreement as to other therapeutic benefits. At least one factor in this disagreement appears to be that of dosage. Up to the second decade of the present century the dosage in common use was, with some exceptions, considerably less than that now usually considered necessary to obtain full therapeutic effects—10 to 12 g. of salicylate a day.

In most of the early reports in which small doses of salicylate were given the general conclusion was that salicylate diminished the intensity and duration of the acute symptoms of the disease but probably increased the likelihood of recurrence. In 1878 Stricker reported that salicylic acid brought relief from discomfort within 2 days to 44 of 60 patients given this drug. In 1881 Hood expressed the opinion that while the principal symptoms were relieved by salicylate, the drug enfeebled the patient so that a longer hospitalization was required than for patients who did not receive salicylate and that relapses were more common.

TABLE 14.—*Production of Salicylic Acid and its Compounds, in Million Pounds, United States 1941-44*

	1941	1942	1943	1944
Salicylic acid	5.3	4.1	5.1	5.5
Acetylsalicylic acid	8.1	8.7	8.7	9.4
Sodium salicylate	1.0	0.7	1.1	1.4
Other salicylic acid salts	0.04	0.02	no data	0.04

In 1883 Badt compared the results in 148 cases of rheumatic fever in which salicylate was given with those in 178 cases in which it was not. His findings indicated that the salicylate relieved discomfort but tended to increase recurrence of the disease and that the incidence of cardiac complications was not significantly affected. In 1877 Moore reported that in his experience salicylate shortened the average stay in the hospital in rheumatic fever from 26.6 to 14.8 days. Warner [1888] supported this finding but reiterated on the observation that salicylate increased the number of relapses.

Owen [1881] reported that there was no decrease in the occurrence of pericardial friction and cardiac murmurs in patients given salicylate. In 1884 May reported a slight lessening of the incidence of cardiac impairment in patients receiving salicylate and in 1888 Hall supported this finding on the basis of his observation that there was the same frequency of this impairment in mild cases of rheumatic fever receiving no salicylate as in severe cases treated with salicylate. He did not give any evidence of the likelihood of cardiac impairment in relation to the severity of the disease when no salicylate was given.

As late as 1907 Steinitz stated that he was unable to see any advantage in the treatment of rheumatic fever with salicylate. In 1911 Menzner compared the results in 86 patients given salicylate with 55 patients given none and found that for the first group the duration of the acute disease was lessened by 30 per cent, the cardiac complications by 38 per cent and the pleurisy by 71 per cent. There was, however, an increase in the number of relapses occurring among the patients given salicylate. In 1914 Miller reported no significant difference in the length of hospitalization of patients receiving salicylates as compared to those who did not. And in 1923 Ehrström and Wahlberg reviewed the histories of a large number of patients with rheumatic fever admitted to the hospital between 1842 and 1920, some of whom had been treated with salicylate and others not. They concluded that the administration of salicylate did not influence the incidence of cardiac complications.

As stated above, the practice of giving large doses of salicylate in the treatment of rheumatic fever became extensive in the second decade of the present century. After this time there is a favorable change in the therapeutic benefits attributed to salicylate, especially in regard to the complications of the disease.

Daniélopou [1923] concluded from his observations that in

patients given large doses of salicylate during the first few days of the disease the incidence of cardiac complications was much lower than when salicylate therapy was instituted too late to check the disease at an early stage. Daniélopolu, Dimitriu and Béranger [1932] later elaborated on these findings with the statement that salicylate in large doses has a curative effect on early heart lesions as long as they are confined to small-cell infiltration with edema and before any scar formation has taken place.

Bertram [1925] reported that patients treated with large doses of salicylate had a considerably lower incidence of cardiac complications than those who received only arsenicals, sedatives and rest. Leech [1930] reported similar favorable results from salicylate therapy. Levy and Turner [1927] reported that in rheumatic fever the P-R interval of the electrocardiogram which had become lengthened was gradually restored to normal by salicylate therapy. Wyckoff, DeGraff and Parent [1930] were unable to confirm this finding. Master and Romanoff [1932] treated 33 patients with salicylate and 30 with other drugs and found that although acute pericarditis occurred only half as frequently in the patients receiving salicylate, there was no decrease in the occurrence of myocardial involvement.

Murray-Lyon [1936] compared the course of rheumatic fever in 139 patients receiving salicylates with 338 receiving none. The average time for disappearance of fever was 3.4 days for those receiving salicylate and 11.2 days for those not receiving it. They recommended that in adults treatment should be started by giving 13 to 16 g. of salicylate daily until toxic effects appeared or until the temperature remained below 99° F. for 24 hours, after which the dose was to be reduced to 10 to 12 g. daily for 10 days, then 8 g. daily for 4 weeks, then 4 g. daily until the patient was allowed out of bed, and finally 2 to 3 g. a day.

Coburn in 1943 reported highly favorable results in the prevention of cardiac complications by the use of large doses of salicylate and made the important contribution of determining dosage on the basis of concentration of salicylate developed in the plasma. He concluded that a salicylate concentration of at least 35 mg. per 100 cc. of plasma was necessary to produce prompt and progressive subsidence of rheumatic inflammation. Although no exact correlation can be established between the amount of salicylate administered

and the concentration developed in the plasma, a daily dose of 10 to 12 g. generally results in about this concentration. Coburn also recommended that the effective concentration in the plasma be attained as rapidly as possible by giving 10 to 20 g. of salicylate intravenously the first 6 days of the treatment and thereafter maintaining a concentration of at least 35 mg. per 100 cc. of plasma by oral administration of salicylate with bicarbonate every 4 hours day and night until 2 weeks after the sedimentation rate has become normal.

Taran, Jacobs and Krautman [1945] have reported results on the prevention of cardiac complications comparing favorably with those found by Coburn from the use of large doses of salicylate. To the contrary, Warren, Higley and Coombs [1945, 1946] observed no difference in the frequency with which murmurs and other cardiac abnormalities occurred in patients treated with small and large doses of salicylate and Wright [1945] expressed the opinion that the treatment of rheumatic fever even with large doses of salicylate does not offer complete protection from cardiac involvement. In 38 of 58 patients given large doses significant murmurs or electrocardiographic changes occurred which in 10 were persistent. Keith and Ross [1945] reported the finding of the same incidence of cardiac involvement among 70 patients given large daily doses of salicylate as among 33 given small doses or none.

There is, however, general agreement among clinicians that the dosage advocated by Coburn gives the greatest possible freedom from cardiac complications. There is somewhat less agreement with the recommendation of intravenous administration. Some clinicians have reported favorably upon its use (753, 1573, 2036, 2329); others believe that it may be dangerous and that with the rapid absorption of salicylate from the gastrointestinal tract it is unnecessary (68, 1364, 1849, 2244, 2963, 3205, 3272, 3437, 3793).

Keith and Ross [1945] reported that although large doses of salicylate diminished the inflammation of the joints, lowered the temperature and reduced the pulse rate in rheumatic fever, the reduction of the sedimentation rate and the prevention of the development of cardiac sequelae were not better than from using small amounts of salicylate. However, these investigators administered the salicylate only during the day and with large amounts of bicarbonate; both of these factors might be expected to result in

periods during which the concentration of salicylate in the plasma would be inadequate, a condition which was, in fact, found to prevail in their patients in the morning.

Comparing the treatment of patients with adequate and subadequate amounts of salicylate Węgrin and Smull [1945] observed no differences in the duration of the disease as judged by the sedimentation rate. However, in the treatment of 64 children with rheumatic fever, Taran, Jacobs and Krautman [1945] found that doses of salicylate sufficiently large to cause a concentration in the plasma of 35 to 45 mg. per 100 cc. resulted in a more rapid and effective subsidence of the disease. They found oral administration to be as effective as intravenous administration.

In surveying the results of salicylate treatment in 1,000 patients Rosenberg [1946] found that the daily oral administration of 10 g. of sodium salicylate with 6 to 8 g. of sodium bicarbonate proved satisfactory. In some refractory cases and in those with gastric intolerance, intravenous administration was the most satisfactory method of therapy. In some instances Manchester [1946] observed dramatic suppression of the acute manifestations of rheumatic fever after intravenous administration of salicylate; otherwise he found that orally administered salicylate controlled the rheumatic infection equally well.

In treating an initial attack of rheumatic fever with large doses of salicylate, Jager and Alway [1946] obtained better results than in treating recurrent attacks. Butt and his associates [1945] likewise observed that polycyclic attacks of rheumatic fever do not respond as well to salicylate therapy as a first acute attack. These findings are in contrast to those of Coburn [1943], half of whose successfully treated patients had had polycyclic attacks. The findings of Butt and his associates may possibly be due to the fact that their patients were given small doses of salicylate for the first 2 weeks of treatment and large doses for the next 2 weeks, followed by abrupt cessation of treatment. Coburn gave large doses immediately and continued treatment as long as the symptoms persisted.

Warren, Higley and Coombs [1945, 1946] studied the results of treatment of acute rheumatic fever with small and large daily doses of salicylate and concluded that although large doses reduce the temperature more quickly than small ones, and hence offer an advantage in the treatment of rheumatic pericarditis, they do not shorten the period of rheumatic activity or prevent the development

of polycyclic attacks any more than small doses. They pointed out that although large doses of salicylate may offer some advantage in the early stage of therapy, the continued administration of large amounts until the sedimentation rate is normal is of questionable value. Inspection of the data reported by these investigators reveals "a fallacy of concealed classification" which escaped their attention in the formulation of their conclusion. Their patients were placed in one of two treatment groups according to well-established clinical principles; mild cases were generally treated with small doses of the drug and severe cases with large doses. Thus 91 per cent of the patients treated with large doses of salicylate were severely ill; only 42 per cent of those treated with small doses were classified as severe. In effect, then, Warren, Higley and Coombs did not actually compare the therapeutic results of small and large doses of salicylates; they compared—essentially, although not clearly—the action of large doses in severe cases to the action of small doses in mild cases. The only conclusion that seems permissible from their data is that treatment with small doses of salicylate was as effective in mild cases of rheumatic fever as treatment with large doses in severe cases.

Although, as stated by Coburn [1943], "salicylate is not the final solution to the therapeutic problem arising in rheumatic fever," it is clear from reports in the literature that suppression of the inflammatory process and prevention of undesirable sequelae are best effected by a quickly established and maintained adequate concentration of salicylate in the plasma.

ADDITIONAL REFERENCES

Prevention or Amelioration of Cardiac Involvement:

883, 1353, 1465, 1722, 1868, 2051, 2167, 2256, 2258, 2264, 2450, 2464, 2735, 2928, 3067, 3269, 3354, 3595, 3715.

Failure in Prevention or Amelioration of Cardiac Involvement:

119, 788, 824, 1060, 1120, 1244, 1285, 1337, 1473, 1577, 1730, 1818, 2244, 2436, 2803, 3296, 3411, 3595, 3630, 3959, 3962, 3978, 3990.

Cardiac Involvements:

338, 450, 584, 701, 722, 894, 1387, 1762, 2221, 2257, 2433, 2514, 2596, 2765, 3343, 3828, 3971, 3990, 4077.

Treatment in Acute Stages of Rheumatic Fever:

SALICIN: [1876] 815, 1446,
2242, 2275, 3530; 306; [1913]
3355.

*Italic figures in brackets identify year of publication.

SALICYLIC ACID: [1875] 2907; [1876] 515, 571, 676, 1089, 1337, 1639, 1698, 2470, 2540, 2655, 2897, 2908, 3377, 3511, 3631, 3847, 3953, 3955, 3956, 3964; [1877] 529, 1559, 1868, 2459, 2609, 2648, 2707, 3002, 3140, 3296, 3852; [1878] 446, 635, 1785, 3299, 3379; [1877-9] 1267; [1879] 2196, 2266; [1881] 1853, 2023; [1882] 3990; [1883] 126; [1884] 3695; [1886] 1170; [1888] 106, 1155, 3816; [1892] 1408; [1895] 901; [1898] 2481; [1903] 1906, 3817; [1904] 230; [1906] 3051; [1907] 3329; [1908] 2439; [1909] 1008; [1913] 3355; [1915] 3813.

SODIUM SALICYLATE: [1876] 515, 1790, 2666, 2908, 3181; [1877] 390, 608, 1559, 1730, 2324, 2648, 3141; [1878] 190, 883, 928; [1881] 2650; [1887] 28, 297; [1888] 1440; [1903] 388; [1904] 229, 465, 2383, 2384; [1905] 2385, 2987; [1906] 3350; [1907] 3515; [1908] 1365, 2049; [1909] 1156; [1911] 1566, 3156; [1912] 857, 1598, 2051, 2259, 3806; [1913] 2436, 2676, 2794, 3355; [1914] 722, 1759, 2617, 3701; [1915] 619, 1512; [1916] 16; [1920] 1576; [1921] 1287, 2221; [1922] 1581, 2098, 2224, 3070; [1923] 807, 1715, 2067, 3819; [1924] 2928; [1925] 276, 569, 1793, 1844; [1926] 289, 599, 603, 2421; [1927] 593; [1929] 2311, 2715, 3442; [1930] 600, 601, 3797; [1931] 267, 597, 602, 809, 2773, 3461; [1932] 810; [1933] 2422; [1934] 116, 1567, 1914; [1935] 584, 585, 680, 3878; [1936] 494, 746, 747, 796, 2515, 3289, 3491; [1937] 2133; [1939] 1005; [1940] 614, 2367, 3568, 3733; [1941] 893; [1942] 664, 695, 968; [1943] 615, 696, 1573, 2239; [1944] 753, 826, 2036, 2136, 3688; [1945] 147, 521, 955, 1364, 1574, 1849, 2244, 2329, 3012, 3437, 3634, 3655, 3793; [1946] 1748, 2294, 2962.

ACETYSALICYLIC ACID: [1899] 1143, 3009, 3756; [1900] 470, 1189, 1244, 1302, 1348, 1413, 1592, 1859, 1964, 2142, 2166, 2291, 2292, 2293, 2351, 2499, 2885, 2996, 3058, 3547, 3659, 3828; [1901] 279, 576, 820, 1345, 2450, 2596, 3066, 3445, 3498; [1902] 1251, 1323, 2400, 3753; [1903] 1118, 1783, 2237, 3418, 3464, 3637; [1904] 465, 2991, 2992; [1905] 503; [1906] 650; [1907] 259; [1909] 1008; [1912] 257, 2259; [1913] 3355; [1914] 1759; [1915] 1512; [1920-2] 1576; [1923] 316; [1926] 1743; [1927] 1762; [1929] 1180, 1465; [1931] 3206; [1932] 3577; [1934] 4077; [1935] 2422; [1936] 1511, 1818, 2248; [1937] 2795, 3185; [1940] 2367; [1943] 615, 2239; [1945] 718, 1849.

METHYL SALICYLATE: [1903] 3817; [1904] 2384; [1906] 3350; [1912] 3806.

PHENYL SALICYLATE: [1887] 228, 1577, 1881, 2690; [1888] 106, 416; [1915] 1512; [1935] 2422.

SALICYLSALICYLIC ACID: [1908] 2439; [1910] 156; [1914] 1975; [1935] 2422.

ACETYL-P-AMINOPHENYL SALICYLATE: [1892] 3993; [1894] 1949; [1895] 2902; [1898] 2481.

Administration by Other than Oral Route:

RECTALLY: (*Sodium salicylate*) 297, 494, 615, 664, 753, 1573, 1576, 1598, 1715, 2221, 2311, 3461; (*Acetylsalicylic acid*) 1180.

EXTERNALLY: (*Salicylic acid*) 230, 1906, 3051, 3816, 3817; (*Sodium salicylate*) 1566; (*Methyl salicylate*) 614, 2384, 3350, 3806, 3817.

BY INJECTION: (*Sodium salicylate*) 16, 388, 569, 593, 619, 722, 746, 748, 753, 955, 1287, 1573, 1581, 1748, 2098, 2133, 2221, 2224, 2244, 2311, 2329, 2383, 2384, 2385, 2676, 2962, 2987, 3012, 3070, 3156, 3437, 3568, 3634, 3793, 3819; (*Acetylsalicylic acid*) 1759.

ATTEMPTED PROPHYLAXIS OF RHEUMATIC FEVER

The prevention of rheumatic fever following tonsillitis by the use of salicylate was advocated by Kieffer (1861) in 1906. He had observed over a period of 38 years that the seasonal and yearly occurrence of these two diseases were parallel and suggested that there was a relationship between them. In 60 patients with tonsillitis he applied acetylsalicylic acid to the tonsils and reported that the average duration of the tonsillitis in these cases was 3 days as compared to 6 days in 60 control cases. In addition, 9 patients in the control group developed rheumatic fever but none in the treated group.

Attention was again directed to the possible prophylactic action of salicylate for rheumatic fever by the work of Derick, Hitchcock and Swift, reported in 1928, on the effect of antirheumatic drugs on the arthritis and on the immune-body production in serum sickness. They found that the prolonged administration of salicylate to patients who had received large amounts of antipneumococcus horse serum usually resulted in the prevention of one of the manifestations of serum sickness—arthritis. They advanced the theory that in serum sickness the arthritis which is the result of passive sensitization of the joints is inhibited when the circulating antibodies in the serum are kept at a low concentration, and that the antirheumatic drugs accomplish this. The suggestion for this theory originated in the earliest investigation by Swift [1920] of the reason for the beneficial effect of sodium salicylate in rheumatic fever. He found that in rabbits immunized with *Streptococcus viridans* or with blood cells, daily administration of sodium salicylate resulted in a diminished number of complement-fixing antibodies.

On the theory that relapses in rheumatic fever following acute tonsillitis are a manifestation similar to the arthritis of serum disease, in which the tonsillitis might have the same effect as injection of serum, Schlesinger [1930] investigated the usefulness of acetylsalicylic acid in the prevention of such relapses. In 16 rheumatic children given salicylate during or immediately after a tonsillitis no serious relapse occurred. He recommended that every rheumatic child be given salicylate at the signs of a cold or throat infection. Successful prevention of serious rheumatic relapses in children with acute tonsillitis was also reported by Poynton and Schlesinger [1937]. On the basis of 7 years' experience, Schle-

singer [1938] reported that recurrences following throat infections were less frequent among patients given salicylate.

Successful prophylactic effects of acetylsalicylic acid on recurrence of rheumatic fever in children with tonsillitis were also reported by Podolsky and Goldstein [1931]. Sheldon [1931], however, was unable to draw any conclusions as to the prophylactic effectiveness of salicylate in 7 rheumatic children, and Perry [1933] could find no evidence, from observation of 41 rheumatic children, that the prolonged administration of salicylate was of value in preventing relapse. In the reports of Sheldon and Perry, however, no reference is made to the presence in their patients of tonsillitis or other throat infection.

Coburn and Moore [1942] observed 186 young patients with rheumatic fever who had hemolytic streptococcal pharyngitis, to 47 of whom salicylate was administered daily. Of those not treated with salicylate 41 per cent developed recrudescence of rheumatic symptoms, as compared with only 2 per cent of those given salicylate.

The successful use of salicylate in the prevention of rheumatic fever relapse following respiratory infections instigated considerable experimental investigation of the mechanism of this action of salicylate. Hagebush and Kinsella [1930] found that sodium salicylate suppressed the allergic dermal reactions of rabbits to filtrates of hemolytic streptococci. Schlesinger and Signy [1933] sought specific precipitins in the blood serum of rheumatic children during the quiescent period following throat infections, using filtrate of ground-up streptococci as the antigen. In no case were precipitins found at the time of the acute throat infection but they did appear between the tenth and thirtieth days after the onset of the tonsillitis, which was the time of or a week prior to the renewed clinical manifestations of rheumatic fever. When precipitins were formed despite medication with acetylsalicylic acid, their appearance was noticeably delayed.

Perry [1939] reported that in 21 rheumatic patients who developed hemolytic streptococcal sore throat during a quiescent period, acetylsalicylic acid inhibited the formation of antifibrinolysin. In normal individuals given 30 to 45 gr. of acetylsalicylic acid daily for 10 days between the first and second antityphoid inoculations, Perry [1941] found no difference in the antibody titer attained in the salicylate-treated and control subjects, but in the

treated group the titer fell to a lower level than in the controls in 8 to 10 weeks.

Because of the belief that the therapeutic action of salicylate in rheumatic fever may result from the inhibition of immunological reactions, Coburn and Kapp [1943] studied the effect of salicylate on the nonspecific precipitation of proteins and the precipitation of antigens by antibodies. They found that precipitation by a non-specific agent, such as sodium tungstate, is inhibited by salicylate. This suggests a combination of the protein with the salicylate. They also found that precipitation of an antigen by its specific antibody was prevented by salicylate presumably because of the inactivation of the antibody.

In patients with acute group-A hemolytic streptococcal sore throat Rantz, Boisvert and Spink [1946] observed no diminishing of the titer of antifibrinolysin and antistreptolysin from salicylate. However, Homburger [1946 (1656)] immunized guinea pigs and rabbits by the injection of red blood cells of the rhesus monkey and found that the formation of anti-Rh agglutinins was diminished when sodium salicylate was administered for 3 days prior to and during the period of immunization. Aikawa [1945], from a review of investigations on the prophylaxis of rheumatic fever, supports the belief that salicylate may block the antigen-antibody reaction which may be a basic feature in this disease.

The clinical and experimental observations reported in the literature are in fair agreement as to the benefits of salicylate in the prophylaxis of rheumatic fever, particularly after acute tonsillitis or other respiratory infections.

ADDITIONAL REFERENCES

154, 1208, 1415, 2469, 3343, 3474, 3716.

CHOREA

The frequent occurrence of chorea in rheumatic fever early led to the theory that these diseases may have a common cause. As a result, salicylate has often been used in the treatment of chorea. Some clinicians have reported favorable results with this use of the drug; others have found it useless. In most instances in which favorable results were obtained, salicylates were credited with alleviating the symptoms and shortening the course of the disease.

Beneficial treatment of chorea has been reported with the use of sodium salicylate (200, 926, 1201, 2049), acetylsalicylic acid (32,

279, 503, 926, 1201, 1251, 1263, 1264, 1323, 2073, 3156, 3158, 3342, 3618, 3729), acetylsalicylic acid combined with magnesium (1818), and calcium acetylsalicylate (23, 2520, 2688).

No beneficial effects from the use of salicylates in chorea were observed by others (3140, 3595, 3745, 3852). McCombs [1943] advised against the use of salicylate in chorea; Tice [1936] doubted the value of this drug in cases without signs of rheumatism; and Meakins [1940] believed that there was no sound reason for the use of salicylate in the treatment of chorea.

Studying the records of 77 patients with chorea, Cockayne [1910] stated that various salicylates did not prevent the development of heart lesions. On the other hand, Bertram [1925], who compared arsenicals, sedatives, salicylates and simple bed rest, found that "cases of chorea treated by sodium salicylate had a lower incidence of subsequent carditis."

Leech [1930] gave 20 gr. of acetylsalicylic acid daily to 67 children with inactive rheumatic heart disease. Six per cent of these had recurrence of choreatic symptoms as compared with 11.4 per cent of 79 children in a control group.

ADDITIONAL REFERENCES

244, 259, 1512, 2710, 3283, 3978.

DIFFERENTIAL DIAGNOSIS OF RHEUMATIC FEVER

Because of its effectiveness as a therapeutic agent in rheumatic fever, the use of salicylate has been advocated for the diagnosis of this disease. In 1905 Mendel administered sodium salicylate intravenously to patients with chronic diseases of the joints. Only in rheumatic patients were the pains relieved immediately and the swelling visibly reduced. In spite of the opinion that this prompt action of salicylate is diagnostic of rheumatic fever Haig [1907] and Stockman [1908] expressed the opinion that failure of salicylate to relieve arthritic pain is no proof that they were not of rheumatic origin. Brian [1922] sought to discourage this use of salicylates for diagnostic purposes in the belief that the diagnosis of syphilitic as well as tubercular arthritis, which may be relieved by salicylates, may be obscured, and the specific treatment for these diseases retarded.

In 1937 Mester (2411, 2412) first described what he called an "immunobiologic specific reaction" of rheumatic fever patients to

salicylic acid. This consisted of a decrease of over 15 per cent in the white blood cell count in rheumatic patients 30 to 60 minutes after intradermal injections of small amounts of salicylic acid. The reaction was described as positive in every kind of rheumatic affliction. Of 17 nonrheumatics, only 1 patient who had inflammation of the joints and pulmonary tuberculosis reacted positively. Lenocho [1938] applied Mester's test to approximately 140 patients; 13 per cent of the rheumatic cases reacted negatively and 30 per cent of the nonrheumatic cases gave a positive reaction. He considered the test as a possible aid in the diagnosis of rheumatic fever but one that was far from infallible. According to Brauch [1944] the test was recommended by Braghin [1939], Liuzzo [1940], Mosonyi [1940] and Schroeder [1942].

There is as much opinion against as in favor of the test. Green and Freyberg [1941] reported that it was unreliable and Copeman and Stewart [1942] and Brendstrup [1943] that it was inadequate in differential diagnosis. Brauch [1944] pointed out that injection even of saline might produce changes in the white blood cell count and concluded that Mester's test was useless for the differential diagnosis of rheumatic and nonrheumatic diseases. Woods and Comroe [1945] reached a similar conclusion.

Hintzelmann and Sirotny [1942] proposed to use the rate of elimination of salicylate as a criterion for the diagnosis of rheumatoid arthritis and rheumatic fever, and as an indication of the severity of the latter. Ten hours after the oral administration of 1 g. of salicylic acid the rate of elimination of salicylate was measured for a subsequent 14-hour period. In 11 cases of rheumatic arthritis the rate of elimination was reported by these investigators to be greatly increased after clinical improvement under salicylate medication. These observations cannot be evaluated at present since the effect of salicylate medication on elimination of the drug in normal control subjects was not studied and since the observations reported have not been corroborated by other investigators.

ANTIPYRESIS

Aside from its specific and antipyretic action in rheumatic fever as discussed in the preceding sections, salicylate has been used solely for its antipyretic action in a wide variety of diseases. With few exceptions, to be noted below, satisfactory antipyresis was obtained. Most of the reports in the literature dealing with antipyresis were

made prior to 1900. It will be sufficient here to list the various conditions and the different salicylates which have been used for this purpose.

Adenitis. Acetylsalicylic acid (2004).

Angina. Salicylic acid (190, 293); sodium salicylate (824, 4079); iron salicylate (2034); salicin (4079).

Arthritis, gonorrheal. Calcium acetylsalicylate (257). It was reported that no antipyresis was obtained with phenyl salicylate (1577) and acetylsalicylic acid (470).

Brain concussion. Acetylsalicylic acid (2004).

Bronchitis. Sodium salicylate (2447); acetylsalicylic acid (3313).

Cholera. Acetyl-p-aminophenyl salicylate (169); phenyl salicylate (3770).

Diphtheria. Salicylic acid (190, 293, 889, 1148, 1149, 1267, 1868, 2682, 2793, 3390, 3613); sodium salicylate (2447). Some observers found no relief from fever in this disease from salicylic acid (1267, 3104, 3613).

Dysentery. Salicylic acid (293); sodium salicylate (1812); phenyl salicylate (2860).

Enteritis. Acetylsalicylic acid (2004, 3753); acetyl-p-aminophenyl salicylate (169).

Erysipelas. Salicylic acid (190, 293, 512, 2648, 2907); acetylsalicylic acid (2562); iron salicylate (2034).

Influenza. Acetylsalicylic acid (470, 1607, 1749, 1783).

Malaria. Salicylic acid (1868, 2907, 3475); acetylsalicylic acid (3498); salipyrine (1409); ammonium salicylate (178); salicin (3485). No effect on the fever was reported by other observers for salicylic acid (190, 293, 1055) and salicin (3183).

Nephritis. Acetylsalicylic acid (2885).

Ovarian cyst, suppurating. Acetylsalicylic acid (287).

Parametritis. Sodium salicylate (2447).

Parotitis epidemica. Salicylic acid (190).

Pneumonia. Salicylic acid (190, 293, 512, 2648, 2907); acetylsalicylic acid (2562); iron salicylate (2034).

Rheumatism. Salicylic acid (190, 293, 512, 2648, 2907); acetylsalicylic acid (2562); iron salicylate (2034); salicin (4079). No decrease of fever in pleurisy after

Pneumonia. Salicylic acid (190, 293, 512, 2648, 2907); acetylsalicylic acid (2562); iron salicylate (2034); salicin (4079).

Puerperal fever. Salicylic acid (264); acetylsalicylic acid (2283); ammonium

Scarlet fever. Salicylic acid (1267, 2029, 2793); sodium salicylate (2847); acetylsalicylic acid (3932); salicin (4079).

Septicemia. Acetylsalicylic acid (899); salicylates in general (680).

Smallpox. Salicylic acid (407, 3692); phenyl salicylate (222, 298). One investigator (3484) found phenyl salicylate to be ineffective.

Stomatitis. Salicylic acid (293).

Trypanosome infection. Sodium salicylate (2468).

Typhoid. Salicylic acid (190, 293, 512, 2648, 2905, 2907, 3183, 3279, 3447, 2648, 2657, 2941); acetylsalicylic acid (2562); iron salicylate (2034); salicin (4079); salipyrine (1409);

salicyl-arsenic (4113).

Typhoid. Salicylic acid (190, 293, 512, 2648, 2905, 2907, 3183, 3279,

3390, 3475, 3732); sodium salicylate (149, 190, 1055, 2446, 2447, 2648); acetylsalicylic acid (287, 368, 1749, 1964, 2004, 3190, 3753); phenyl salicylate (1577); salicin (3183); ammonium salicylate (178). Acetylsalicylic acid (2885), diaspirin and salicylsalicylic acid (368) have been reported to be ineffective in the treatment of this fever, and the danger of anuria (1699) and delirium (717) from the use of salicylic acid in typhoid has been pointed out.

Yellow fever. Salicylic acid (498, 1153).

ANALGESIA

The widest use of salicylate, particularly acetylsalicylic acid, is for the safe relief of pain of moderate intensity, especially headache and muscular pain.

Salicylic acid has been recommended for the relief of pain in neuralgia and sciatica (1267, 3140).

Sodium salicylate has some use for relief of pain in neuritis and sciatica (388, 4077) and in migraine and simple headache (259, 3140). Daniélopou and Crivetz [1946] recently recommended treatment of migraine with sodium salicylate since the action of histamine, which plays an important part in migraine, is inhibited by salicylic acid and sodium salicylate. They reported excellent results with a daily dose of 6 g. of sodium salicylate with sodium bicarbonate given for 10 days each month.

Acetylsalicylic acid has been reported upon for the relief of pain in the following disturbances:

Neuralgia: 470, 650, 820, 843, 1143, 1189, 1207, 1244, 1251, 1307, 1345, 1413, 1592, 1743, 1921, 1964, 2061, 2291, 2398, 2517, 2562, 2596, 2658, 2845, 2948, 2982, 3066, 3498, 3517, 3547, 3659, 3750, 3828.

Sciatica: 257, 430, 470, 1143, 1189, 1251, 1581, 1743, 1964, 2061, 2167, 2400, 2596, 2885, 3066, 3418, 3478, 3489, 3517, 4077.

Migraine and simple headache: 257, 259, 470, 843, 988, 1054, 1143, 1207, 1307, 1743, 1783, 1879, 1921, 2291, 2351, 2374, 2499, 2517, 2596, 2845, 3009, 3397, 3464, 3489, 3498, 3499, 3750, 3828, 3943.

Dysmenorrhea: 1328, 1743, 1783, 1879, 2398, 2991, 3464, 3498.

Genito-urinary disturbances: 3381.

Backache: 2351, 2499, 3009.

Renal calculus: 1663.

Tabs and syphilitic periostitis: 470, 540, 3488, 3659.

Earache: 2374, 3498, 3499.

Toothache: 2562, 2845, 3498, 3541.

Cancer: 259, 437, 820, 1039, 1143, 1345, 2398, 2998, 3066, 3498, 3659, 3660, 3750.

In the only instance reported of the use of this drug in sacrodynia (3397) no relief from pain was obtained.

The use of salicylates, especially acetylsalicylic acid, for the relief of pain in muscular rheumatism, lumbago and myalgia has been

made prior to 1900. It will be sufficient here to list the various conditions and the different salicylates which have been used for this purpose.

Adenitis. Acetylsalicylic acid (2004).

Angina. Salicylic acid (190, 293); sodium salicylate (824, 4079); iron salicylate (2034); salicin (4079).

Arthritis, gonorrheal. Calcium acetylsalicylate (257). It was reported that no antipyresis was obtained with phenyl salicylate (1577) and acetylsalicylic acid (470).

Brain concussion. Acetylsalicylic acid (2004).

Bronchitis. Sodium salicylate (2447); acetylsalicylic acid (3313).

Cholera. Acetyl-p-aminophenyl salicylate (169); phenyl salicylate (3770).

Diphtheria. Salicylic acid (190, 293, 889, 1148, 1149, 1267, 1868, 2682, 2793, 3390, 3613); sodium salicylate (2447). Some observers found no relief from fever in this disease from salicylic acid (1267, 3104, 3613).

Dysentery. Salicylic acid (293); sodium salicylate (1812); phenyl salicylate (2860).

Enteritis. Acetylsalicylic acid (2004, 3753); acetyl-p-aminophenyl salicylate (169).

Erysipelas. Salicylic acid (190, 293, 512, 2648, 2907); acetylsalicylic acid (2562); iron salicylate (2034).

Influenza. Acetylsalicylic acid (470, 1607, 1749, 1783).

Malaria. Salicylic acid (1868, 2907, 3475); acetylsalicylic acid (3498); salipyrine (1409); ammonium salicylate (178); salicin (3485). No effect on the fever was reported by other observers for salicylic acid (190, 293, 1055) and salicin (3183).

Nephritis. Acetylsalicylic acid (2885).

Ovarian cyst, suppurating. Acetylsalicylic acid (287).

Parametritis. Sodium salicylate (2447).

Parotitis epidemica. Salicylic acid (190).

Pertussis. Acetylsalicylic acid (2004, 2991).

Pleurisy. Salicylic acid (293, 512); sodium salicylate (2447, 3313); acetylsalicylic acid (470, 797, 2004, 3313, 3753); acetyl-p-aminophenyl salicylate (169). One investigator (2885) reported no decrease of fever in pleurisy after giving salicylic acid.

Pneumonia. Salicylic acid (190, 293, 1267, 2029, 2793, 2847); acetylsalicylic acid (190, 2447, 2648); iron salicylate (2034).

Puerperal fever. Salicylic acid (2648); acetylsalicylic acid (2283); ammonium salicylate (178).

Scarlet fever. Salicylic acid (1267, 2029, 2793); sodium salicylate (2847); acetylsalicylic acid (3932); salicin (4079).

Septicemia. Acetylsalicylic acid (899); salicylates in general (680).

Smallpox. Salicylic acid (407, 3692); phenyl salicylate (222, 298). One investigator (3484) found phenyl salicylate to be ineffective.

Stomatitis. Salicylic acid (293).

Trypanosome infection. Sodium salicylate (2468).

Tuberculosis. Salicylic acid (190, 293, 398, 512, 1315, 1522, 2648, 2905, 3183); acetylsalicylic acid (2004, 2991); iron salicylate (2034); salicin (4079).

Of 110 patients who were given only a placebo, 35 per cent reported improvement.

Acetylsalicylic acid, as these findings tend to show, probably exerts little specific action on the infections of the upper respiratory tract but it is widely and beneficially used in these infections for symptomatic relief of the pain in the throat, muscular aches and general discomfort incident to the infection.

Diseases of the lungs and pleurae. The use of various salicylates has been reported upon, particularly in the older literature, for the treatment of pneumonia (39, 85, 404, 576, 2907, 3138), pulmonary gangrene (274, 293, 3140), bronchitis with fetid sputum (3869) and pulmonary emphysema (2073). Intravenous administration of sodium salicylate has been recommended for the treatment of pneumonia (765) and pleurisy (2987). Acetylsalicylic acid has been used in the treatment of painful dry pleurisy (39, 470, 1143, 1323, 2400, 2499, 2572, 2596, 3066, 3354, 3749, 3828), and also acetyl-p-aminophenyl salicylate, sodium acetylsalicylate and salicylic acid (169, 230, 257, 512, 1043).

Salicylates have been reported to enhance the reabsorption of exudates of pleurae as well as of other serous cavities (316, 503, 1364, 1365, 2004, 3464), and it has been stated that the salicylate salts are more effective than acetylsalicylic acid (2167).

Influenza. In order to diminish the discomfort and muscular pains in influenza, acetylsalicylic acid (503, 650, 1040, 1118, 1182, 1189, 1251, 1348, 1607, 1749, 1783, 1879, 2293, 2553, 3464, 3547, 3670) and other salicylates (892, 935, 1040, 1182, 1766, 2537, 3770) have been widely used. Neilson [1921] reported favorable symptomatic results with intravenous administration of 5 g. of sodium salicylate in many cases of influenza. This drug, he reported, did not produce the depression, sweating and lowered blood pressure which he observed after medication with acetylsalicylic acid.

Sympton [1903] reported that he obtained no relief with acetylsalicylic acid in the treatment of muscular pain in influenza.

Gastrointestinal disorders. The use of salicylates has been reported for the treatment of gastrointestinal disorders (169, 274, 293, 316, 503, 1749, 1761, 2229, 3613, 3842).

Diseases of the central nervous system. Sodium salicylate given intravenously has been reported upon in the treatment of epidemic encephalitis (187, 244, 568, 569, 646, 762, 1793, 3564), dis-

extensively reported (119, 181, 189, 230, 316, 388, 470, 503, 680, 796, 826, 840, 892, 899, 1118, 1214, 1238, 1251, 1267, 1413, 1545, 1620, 1743, 1783, 1820, 1890, 2049, 2073, 2167, 2291, 2298, 2351, 2400, 2493, 2499, 2766, 2951, 2987, 2991, 3020, 3040, 3066, 3129, 3140, 3230, 3255, 3289, 3355, 3400, 3414, 3418, 3445, 3498, 3499, 3547, 3680, 3691, 3708, 3756, 3806, 3817, 3822, 3827).

Other salicylates, often in conjunction with other analgesic drugs, have been reported upon for the relief of pain in neuralgia (23, 122, 352, 425, 892, 1040, 1203, 1879, 1949, 3468); sciatica (892, 1203, 1761); migraine and simple headache (23, 122, 425, 684, 1039, 1761, 3468); dysmenorrhea (146, 352, 1039, 1040, 1619, 2399, 3598); and other disturbances (169, 425, 1039, 1761, 2399, 3667).

As early as in the first century Dioscorides (896) used salicylate for gout and podagra, as did Quintus Serenus Samonicus (3186). This drug has since been frequently recommended for the treatment of this disease in which its action has probably been primarily that of an analgesic (119, 390, 1214, 2109, 2400, 2440, 2991, 2992, 3140, 3185, 3400, 3750, 3819). Jackson and Blackfan [1907], who like others thought that sodium salicylate increased the formation of uric acid, advised against the use of this drug in gout.

Inflammation of the upper respiratory tract. The use of salicylates has been recommended in tonsillitis and pharyngitis (316, 503, 826, 1100, 1203, 1269, 1365, 1512, 1592, 2034, 3354), in common colds (181, 1059, 1511, 2248, 2304, 2982, 3225), and before and after tonsillectomy. Singer [1945] and Neivert [1945] have pointed out the possible danger of bleeding from the continued use of acetylsalicylic acid after tonsillectomy (see Chapter IV). The intravenous use of sodium salicylate in laryngitis was advocated by Rubens [1905]. Angina, stomatitis and diphtheria have been treated with salol (3163), or by local application of salicylic acid solutions (293); and snuff containing acetylsalicylic acid has been used for rhinitis (1195, 1509). Diehl [1933] investigated the action of acetylsalicylic acid, and of a mixture of this drug with caffeine, on colds. Of 53 patients receiving acetylsalicylic acid alone (5 gr. every 2 hours the first day, and 5 gr. 3 times daily on the following days), 42 per cent reported improvement. Thirty-seven per cent of 53 patients receiving the mixture were also relieved.

phrenia and epilepsy (2518), in cholera asiatica (2205), in gall bladder diseases (629, 2572, 2837, 4077), as antiemetics (777), for vaginal douches (1360), in peritonitis (1427), for yellow fever prophylaxis (3991), in tetanus (519), as anaphrodisiacs (1954), in nycturia (508), for tapeworm (2991), in anaphylactic accidents in serotherapy (809), in dysentery (274), in cystitis and prostatic hypertrophy (2499), in exophthalmic goiter (283), in chronic diarrhea (1267), for deodorizing bowels (3989), in the treatment of abscess (1125), and as a hemostyptic (3390). Salicylates formerly used in mouthwashes are no longer recommended for this purpose because of possible effect on enamel of the teeth (280). Favorable results have been reported in two cases of Still's disease from intravenous administration of sodium salicylate (1252, 2075).

Hypnotic and sedative. A slight hypnotic or sedative action has been reported for salicylic acid (512, 2648, 3072) and acetylsalicylic acid (33, 802, 2061, 2991, 3009, 3691).

Antitussive. The use of acetylsalicylic acid has been reported upon in the relief of coughing spells in whooping cough (2991), asthma (39), and other conditions (988, 1607).

ADDITIONAL REFERENCES

Use in Miscellaneous Conditions:

148, 292, 316, 437, 470, 503, 563, 627, 802, 861, 965, 1143, 1267, 1279, 1343, 1348, 1360, 1413, 1425, 1427, 1764, 1950, 1954, 2291, 2781, 2784, 3009, 3140, 3498, 3499, 3513, 3544, 3659, 3663, 3692, 3750, 3753, 3828, 3925, 4070, 4088.

TOPICAL USES

Although salicylic acid and various of its compounds have been used externally because of their keratolytic action and, to a lesser extent, because of cutaneous absorption of salicylate, methyl salicylate is so irritating to the skin that its wide use in the form of salves and liniments has been reserved only for cutaneous counter-irritation in relieving painful muscles or joints (826, 840, 893, 1214, 2298, 3020, 3289, 3689, 3691, 3779). Some cutaneous absorption of this compound may also occur but any benefit it affords is due mainly to its local irritating action.

Local anesthesia. Acetylsalicylic acid has been used locally after tonsillectomy and in cases of acute pharyngitis (1544) as previously mentioned.

seminated sclerosis (3140) and in some forms of meningitis and myelitis (226, 3009). It is reported that headache and pressure symptoms after apoplexy have been relieved by acetylsalicylic acid (2991).

Diseases of the eye. Systemic medication with various salicylates has been used in the treatment of nonspecific or post-traumatic inflammation of iris, ciliary body, sclera and episclera (34, 1280, 1281, 1512, 3764, 3773), retrobulbar affections (1280), glaucoma (1280, 1512), herpes of cornea (1280, 3773), interstitial keratitis (540, 1280, 3773) and rheumatic iritis (34, 503, 820, 1164, 1243, 1512, 3354, 3773). Good results were reported in the treatment of sympathetic ophthalmia with large amounts of sodium salicylate (34, 545, 1279, 1280, 1281, 1591, 2035, 2144, 2487, 3696, 3731, 3773).

ADDITIONAL REFERENCES

Analgesia, General:

23, 104, 119, 122, 230, 285, 314, 371, 540, 624, 826, 839, 1040, 1203, 1512, 1544, 1545, 1559, 1577, 1581, 1761, 1779, 1906, 1921, 2016, 2101, 2246, 2298, 2307, 2823, 2893, 3156, 3445, 3661, 3698, 3828.

Gout:

155, 975.

Upper Respiratory Tract:

190, 321, 2069, 2731, 2984, 3167, 3498.

Lungs and Pleurae:

184, 288, 291, 388, 600, 1125, 1214, 3991.

Central Nervous System:

242, 512, 1906, 2657, 2669.

Eyes:

1199, 1283, 3123.

MISCELLANEOUS CONDITIONS AND USES

The therapeutic use of salicylates has been reported in a variety of other diseases and conditions but as with many of the maladies mentioned in the preceding sections, the frequency of report does not indicate sound therapeutic procedure or use which is current in modern therapy. They have been used in diabetes (190, 555, 985, 986, 989, 1151, 1174, 1353, 1644, 1821, 1835, 1913, 2022, 2427, 2494, 2503, 2566, 2589, 2590, 2714, 3008, 3289, 3457, 3727, 3728, 3933), in venereal diseases (411, 1764, 2326), in schizo-

of varicose veins was first used by Sicard, Paraf and Lermoyez [1922]. In a large number of patients with varicose veins treated in this way by injection of 20-per-cent sodium salicylate solution Hanschell [1928] found that sloughing sometimes occurred in spite of carefully performed intravenous injection. McPheeters and Rice [1928] attributed this sloughing to perivascular injection and observed painful cellulitis due to passing of the salicylate through the vein wall by osmosis. In a discussion (29, 220, 2268) of the advantages and disadvantages of intravenous sodium salicylate injections for the treatment of varicose veins, it has been pointed out that serious consequences have rarely been reported from the use of this procedure. The pain produced by accidental paravenous injection has served as a warning signal.

Although Kilbourne [1930] stated that sodium salicylate produces sloughing more easily than other drugs used for the treatment of varicose veins, Sicard and Gaugier [1931] pointed out that the local cramps observed immediately after the injection are not dangerous symptoms, and that perivascular inflammation is a sign of rapid healing and is of no serious consequence. In several thousand patients injected with 20- to 50-per-cent solutions of sodium salicylate, the latter investigators observed no dangerous symptoms.

Besides simple solutions of sodium salicylate for the treatment of varicose veins, a mixture of salicylic acid and caffeine (1377), a solution of 15 per cent sodium salicylate in 50-per-cent dextrose (875), and a solution of 30 per cent lithium salicylate with 1 per cent tutocaine (877) have been used for this purpose.

Other topical uses. Salicylates have been used locally for the treatment of wounds and in minor surgery (18, 88, 387, 616, 995, 1267, 1561, 1875, 3613, 3654), in angina and pharyngitis (263, 1100, 1267), in diphtheria (995, 1149, 1267, 3613, 3692, 3732), for vaginal douches and treatment of ulcers of the uterus (616, 1267, 1950), and in conjunctivitis (1267).

ADDITIONAL REFERENCES

Topical Use:

293, 297, 327, 534, 668, 784, 796, 1820, 1905, 2071, 2216, 3276, 3456.

Analgesic effects of small quantities of powdered acetylsalicylic acid after dental extractions and in sores in the mouth caused by friction of dentures have been reported (2823).

Saligenin in 4-per-cent solution has been used successfully as a local anesthetic for the female urethra (1625).

Diseases of the skin. The use of salicylate has been reported in a great variety of skin diseases. Because of the keratolytic action of this drug, it has been used in the treatment of callosities, hyperkeratosis, and ichthyosis (893, 1005, 1512, 1514, 1539, 1540, 1771, 2272, 2712, 3020, 3072, 3289, 3404, 3538, 3691, 3779). Psoriasis has been treated by local (283, 503, 1539, 2272, 3020, 3404, 3538) as well as by intravenous administration (1579, 1646, 1677, 1678, 2223, 2287, 3013, 3268) of sodium salicylate. The topical application of salicylate has also been reported upon in the treatment of acne necrotica (2272), acne vulgaris (893, 2272), alopecia (1514, 3077, 3289), dandruff (680), Darier's disease (2272), exfoliative dermatitis (680), eczema (283, 988, 1539, 2272, 2910, 3289, 3613), erysipelas (2034), erythema nodosum (3354, 3414), erythrasma (2272), favus (1539, 2272), fungus infections (292, 680, 893, 1539, 1681, 2200, 2272, 3404, 3456), furunculosis (263, 1540, 1771, 2414, 3289), gonorrhea (1267), hyperhidrosis (274, 283, 893, 1514, 1539, 1540, 1771, 2272, 3289, 3691), impetigo contagiosa (263, 1540, 1771, 2272), lichen planus (1502, 1539, 2272, 3404) and lichen ruber (2272), lupus erythematosus (2272) and lupus vulgaris (2272), mustard oil inflammation (2472), pediculosis capitis (2272), pityriasis versicolor (691, 893, 2272, 3289), poison ivy (283), pruritus (283, 316, 1267, 1539, 1771, 2272, 3939), seborrheic dermatitis (1514, 1771, 2272), scleroderma (2272), cancer of the skin (3663), tuberculosis of the skin (316, 2272), sycosis (2272), ulcer molle (3420), urticaria (3289, 3404), and verruca vulgaris and senilis (2217, 2272).

Protection against sunburn. Salicylates have been used locally as screens against sunburn. Giese and Wells [1946] stated that the benzene rings and double bonds result in absorption of the erythema-producing rays of sunlight. Bachem and Fantus [1939] found menthyl salicylate to be an efficient sunscreen. Luckiesh, Taylor, Cole and Sollmann [1946] reported that phenyl salicylate in ointment was more effective than menthyl salicylate.

Varicose veins. The injection of salicylate for the obliteration

of varicose veins was first used by Sicard, Paraf and Lermoyez [1922]. In a large number of patients with varicose veins treated in this way by injection of 20-per-cent sodium salicylate solution Hanschell [1928] found that sloughing sometimes occurred in spite of carefully performed intravenous injection. McPheeters and Rice [1928] attributed this sloughing to perivascular injection and observed painful cellulitis due to passing of the salicylate through the vein wall by osmosis. In a discussion (29, 220, 2268) of the advantages and disadvantages of intravenous sodium salicylate injections for the treatment of varicose veins, it has been pointed out that serious consequences have rarely been reported from the use of this procedure. The pain produced by accidental paravenous injection has served as a warning signal.

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Besides simple solutions of sodium salicylate for the treatment of varicose veins, a mixture of salicylic acid and caffeine (1377), a solution of 15 per cent sodium salicylate in 50-per-cent dextrose (875), and a solution of 30 per cent lithium salicylate with 1 per cent tutocaine (877) have been used for this purpose.

Other topical uses. Salicylates have been used locally for the treatment of wounds and in minor surgery (18, 88, 387, 616, 995, 1267, 1561, 1875, 3613, 3654), in angina and pharyngitis (263, 1100, 1267), in diphtheria (995, 1149, 1267, 3613, 3692, 3732), for vaginal douches and treatment of ulcers of the uterus (616, 1267, 1950), and in conjunctivitis (1267).

ADDITIONAL REFERENCES

Topical Use:

293, 297, 327, 534, 668, 784, 796, 1820, 1905, 2071, 2216, 3276, 3456.

Salicylate Poisoning

SINCE the salicylates are among the most widely used of all drugs, and often in large doses, it would be anticipated that reports of poisoning, particularly nonfatal poisoning, would be abundant. Such, however, is not the case. The largest doses of salicylate are used in the treatment of rheumatic fever and the appearance of mild toxic symptoms during such therapy is often accepted as indicative only of adequate salicylate dosage and hence receives no mention. In spite of the large amounts administered repeatedly in the treatment of this disease there are few reported instances of fatalities from this use. In contrast to the disregard of mild toxic symptoms in such therapy is the uncertainty attaching to the word "poisoning" in reports of other uses of salicylates; here poisoning may be applied indiscriminately to effects ranging from mild vertigo and tinnitus to serious collapse and coma. And finally, in many of the reported fatalities from salicylate there is no certainty that the death which was attributed to the drug was not in reality due to the disease for which it was given.

The reports of poisonings and fatalities attributed to salicylate fall into three categories: (1) Records of the U. S. Bureau of the Census; (2) summary reports of poisonings; and (3) reports of individual cases of poisoning.

RECORDS OF THE UNITED STATES BUREAU OF THE CENSUS

From these records data are available on the number of deaths reported as due to salicylate for the years 1926, 1928, and 1930 through 1943, from those states admitted to the Death Registration system. Since 1933 this Registration has included the 48 states. The data from these records are summarized in Tables 15, 16 and 17 as number of deaths and rate per million deaths for males, females and total population and for acetylsalicylic acid, methyl salicylate, other salicylates and all salicylates. Deaths due to sodium salicylate are included in the small group of "other salicylates."

No significant trend in the death rate from salicylate poisoning is apparent. The rate for all salicylates is approximately 50 per cent higher in men than in women. This difference is due largely to the

preponderance in the males of deaths from methyl salicylate, a feature which will be discussed later.

The average annual death rate from salicylate poisoning, as seen from Tables 15, 16 and 17, is not high. During the period 1939 through 1943 there was in the United States an annual mortality of 1,267 due to accidental poisoning by all solids and liquids, of which 4 per cent was attributed to salicylates. The lowness of the figure has particular significance because of the extensive use and wide availability of salicylate compounds.

The deaths due to acetylsalicylic acid represent approximately one-third of the mortality from all salicylates and the rate in the male population is about 20 per cent higher than in the female.

There are significant differences among the various age groups in the number of fatalities attributed to acetylsalicylic acid as well as to methyl salicylate and other salicylates. The number of fatalities recorded for different age classes and for the various salicylate compounds during the period 1933-43 are summarized in Table 18. The corresponding mortality rates are shown in Figure 19. There is a relatively high mortality rate in children between the ages of 1 and 4 years. The mortality drops to a low level in the age class 5 to 14 and rises in the succeeding age groups. The high mortality rate in the age class under 5 years is not due to an especial toxicity of salicylates for children since this group exhibits the same relatively high mortality from poisonings by all solids and liquids. It seems probable that fatal poisonings in children are due largely to medication by ignorant parents and especially, under lack of supervision, to the proneness of children of this age to swallow any readily available object. The rate of death from all poisonings by solids and liquids among Negro children up to the age of 4 years is several times higher than among white children.

During the years 1926, 1928, and 1930 through 1943, the U. S. Bureau of the Census recorded 427 deaths from methyl salicylate (Tables 15, 16 and 17). The methyl salicylate mortality rate was twice as high in men as in women. This marked sex difference in poisoning by methyl salicylate might be explained in adults by the reported use of this compound as a substitute for alcohol in intoxicating beverages (871, 2742). The higher incidence of inebriety among men than women in this country supports this suggestion. Of 37 cases of fatal methyl salicylate poisoning reviewed by Laforet and Collins [1946] 65 per cent were in males, and in one-third of

TABLE 15.—*Accidental Deaths from Salicylates: Number and Rate per Million Male Population**

Year	Male Popu- lation in Millions	ACETYLSALI- CYLIC ACID		METHYL SALICYLATE		OTHER SALICYLATES		ALL SALICYLATES	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate
1926	52.7	11	0.209	16	0.304	1	0.019	28	0.531
1928	57.6	6	0.104	10	0.174	0	0	16	0.278
1930	59.3	5	0.084	20	0.337	1	0.017	26	0.438
1931	59.7	7	0.117	13	0.218	0	0	20	0.335
1932	60.1	8	0.133	14	0.233	0	0	22	0.366
1933	63.4	10	0.158	12	0.189	0	0	22	0.347
1934	63.8	9	0.141	9	0.141	1	0.016	19	0.298
1935	64.2	5	0.078	21	0.327	1	0.016	27	0.421
1936	64.5	12	0.186	25	0.388	2	0.031	39	0.605
1937	64.9	9	0.139	20	0.308	2	0.031	31	0.478
1938	65.3	9	0.138	19	0.291	1	0.015	29	0.444
1939	65.8	5	0.076	20	0.304	2	0.030	27	0.410
1940	66.1	8	0.121	25	0.378	1	0.015	34	0.514
1941	66.7	5	0.075	21	0.315	2	0.030	28	0.420
1942	66.7	8	0.120	20	0.300	3	0.045	31	0.465
1943	68.0	9	0.132	20	0.394	1	0.015	30	0.441
Totals		126		285		18		429	
Averages			0.125		0.283		0.018		0.425

TABLE 16.—*Accidental Deaths from Salicylates: Number and Rate per Million Female Population**

Year	Female Popu- lation in Millions	ACETYLSALI- CYLIC ACID		METHYL SALICYLATE		OTHER SALICYLATES		ALL SALICYLATES	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate
1926	51.2	6	0.117	6	0.117	4	0.078	16	0.313
1928	56.1	8	0.143	11	0.196	0	0	19	0.339
1930	57.9	4	0.069	6	0.104	1	0.017	11	0.190
1931	58.4	5	0.086	4	0.068	0	0	9	0.154
1932	58.8	3	0.051	3	0.051	2	0.034	8	0.136
1933	62.2	9	0.145	7	0.113	0	0	16	0.257
1934	62.6	4	0.064	9	0.144	2	0.032	15	0.240
1935	63.1	3	0.048	8	0.127	2	0.032	13	0.206
1936	63.5	9	0.142	7	0.110	0	0	16	0.252
1937	64.0	4	0.063	13	0.203	0	0	17	0.266
1938	64.5	8	0.124	16	0.248	4	0.062	28	0.434
1939	65.1	11	0.169	9	0.138	2	0.031	22	0.338
1940	65.6	10	0.152	12	0.183	5	0.076	27	0.412
1941	66.4	3	0.045	10	0.151	2	0.030	15	0.226
1942	67.1	3	0.045	13	0.194	1	0.015	17	0.253
1943	68.0	11	0.162	8	0.118	4	0.059	23	0.338
Totals		101		142		29		272	
Averages			0.102		0.143		0.021		0.274

*Data from the U. S. Bureau of the Census.

TABLE 17.—*Accidental Deaths from Salicylates: Number and Rate per Million Total Population**

Year	Total Popu- lation in Millions	ACETYL SALI- CYLIC ACID		METHYL SALICYLATE		OTHER SALICYLATES		ALL SALICYLATES	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate
1926	103.8	17	0.164	22	0.212	5	0.048	44	0.424
1928	113.6	14	0.123	21	0.185	0	0	35	0.308
1930	117.2	9	0.077	26	0.222	2	0.017	37	0.316
1931	118.1	12	0.102	17	0.144	0	0	29	0.246
1932	118.9	11	0.093	17	0.143	2	0.168	30	0.252
1933	125.6	19	0.151	19	0.151	0	0	38	0.303
1934	126.4	13	0.103	18	0.142	3	0.024	34	0.269
1935	127.3	8	0.063	29	0.228	3	0.024	40	0.314
1936	128.1	21	0.164	32	0.250	2	0.016	55	0.429
1937	128.8	13	0.101	33	0.256	2	0.016	48	0.373
1938	129.8	17	0.131	35	0.270	5	0.039	57	0.439
1939	130.9	16	0.122	29	0.222	4	0.031	49	0.374
1940	131.7	18	0.137	37	0.281	6	0.046	61	0.463
1941	133.1	8	0.060	31	0.233	4	0.030	43	0.323
1942	133.8	11	0.082	33	0.247	4	0.030	48	0.359
1943	136.0	20	0.147	28	0.206	5	0.037	53	0.390
Totals		227		427		47		701	
Averages			0.113		0.213		0.023		0.350

TABLE 18.—*Accidental Deaths from Salicylates by Age Classes, United States, 1933-43**

Age Class	Acetylsalicylic Acid	Methyl Salicylate	Other Salicylates	All Salicylates
Under 1	5	6	1	12
1- 4	57	218	11	286
5- 9	4	6	0	10
10-14	0	0	0	0
15-19	7	4	2	13
20-24	4	3	1	8
25-29	5	4	2	11
30-34	7	5	5	17
35-39	18	6	3	27
40-44	12	11	2	25
45-49	9	12	3	24
50-54	9	10	4	23
55-59	6	9	3	18
60-64	8	12	1	21
65-69	4	6	0	10
70-74	2	4	0	6
75-79	5	6	0	11
80-84	1	1	0	2
85 and over	1	1	0	2
Totals	164	324	38	526

*Data from the U. S. Bureau of the Census.

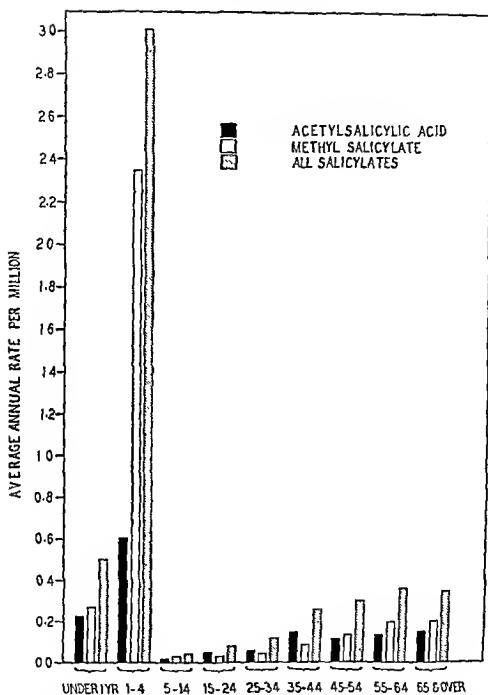


FIGURE 19.—Average death rates per million, by age classes, from accidental poisoning by salicylates in the United States, 1933-43. Based on data of the U. S. Bureau of the Census.

the males over 21 years of age there was a "positive history of alcoholism."

From 1933 to 1943, the U. S. Bureau of the Census recorded 224 deaths due to methyl salicylate in children under 5 years of age and an average annual mortality rate 25 times higher than that of the remainder of the population (Table 18 and Figure 19). The comparatively high mortality from methyl salicylate among children may be explained by the fact that this compound is tempting to children because its odor is that of the wintergreen flavor of candy and soft drinks.

The number of fatalities due to salicylates other than acetylsalicylic acid and methyl salicylate, as recorded by the U. S. Bureau of the Census during the years 1926, 1928 and 1930 to 1943, represents only approximately 7 per cent of all recorded deaths attributed to salicylate (Tables 15, 16 and 17). The distribution of such deaths among the various age groups in the period 1933-43, however, resembles that of the other salicylates, with the largest number occurring in the age class 1-4 years.

Among all the instances of death reported to the U. S. Bureau of the Census there have undoubtedly been many in which a fatal disease or other cause of death was present, so as to render the toxic symptoms of salicylate only incidental. If, in such cases, the certifying physician reports an acute or chronic disease or some other factor as the primary cause of death and salicylate as a contributory cause, salicylate poisoning will nevertheless always be recorded as the primary cause in the official statistics of the Bureau of the Census. This procedure is in accord with the rules governing the statistical handling of death certifications.* Acute poisoning with solids and liquids supersedes all other causes except other concomitant causes of violent death. Thus over-reporting of deaths due to salicylate is more likely than under-reporting.

SUMMARY REPORTS OF POISONINGS

In 1798 Longmore described methyl salicylate poisoning in 14 men of the Royal Artillery at Quebec who drank tea made of three herbs (Ledum, Andromeda and Gaultheria). The symptoms were those of poisoning by oil of wintergreen contained in the Gaultheria. Vertigo, confusion, nausea and vomiting, irregular pulse, perspiration and coma occurred. There were no fatalities.

*Cf. *Manual of Joint Causes of Death* (4th ed., Washington, 1940).

The *American Journal of Pharmacy* (3840) in 1834 reported an unstated number of fatalities due to an oil prepared from Gaultheria which was used for treating dyspepsia, dropsy and gravel.

In 1884 May reviewed the records of 192 rheumatic patients treated with salicylates (189 with salicylic acid and 3 with sodium salicylate). Toxic symptoms including nausea and vomiting, diarrhea, delirium, tinnitus and vertigo were reported in 28 of these patients.

Muller [1904] applied bornyl salicylate (Salit) externally in 36 patients and in a few observed an itchy eczema which spread and, in one instance, covered the entire body.

In 1905 Quenstedt studied the urine of 25 patients receiving 2 to 6 g. of sodium salicylate daily. He reported finding albumin, casts, and red blood cells which disappeared on withdrawal of the drug but in one instance persisted for 2 weeks.

Hanzlik [1913] summarized the clinical records of approximately 400 patients in whom toxic symptoms appeared after administration of various salicylate compounds and from them estimated the doses of salicylate causing such symptoms. For synthetic sodium salicylate his estimate was 11.7 g. for men and 9.1 g. for women; for natural sodium salicylate the values were respectively 13 and 8.8 g.; for methyl salicylate, 7.4 g.; for acetylsalicylic acid, 10.7 and 7.8 g.; and for salicylsalicylic acid, 6.5 and 5.4 g.

The hospital records of 124 rheumatic children were examined by Miller in 1913. Sodium salicylate had been given to these children with sodium bicarbonate. Vomiting occurred in about half of the cases.

In 1930 Balázs reviewed 752 cases of poisoning by acetylsalicylic acid at a hospital in Budapest, Hungary. Four cases terminated fatally, the minimum lethal dose being between 30 and 40 g. The following symptoms were observed as characteristic of salicylate poisoning: dizziness, tinnitus, deafness, nausea, vomiting, fever, prostration, rapid pulse, profuse perspiration in severe cases sometimes accompanied by lowering of temperature, restlessness and coma. In severe poisoning there was also a decrease in the alkali reserve of the blood, presence of albumin, casts and red blood cells in the urine, and frequently acetone in the urine. Balázs reported that in Budapest during the 3-year period 1927-29 the rescue squads were called in 590 suicidal attempts with acetylsalicylic acid.

Odin [1932] reported 27 cases of poisoning by various sali-

cylates. The concentrations of salicylate in the blood ranged from 20 to 47 mg. per 100 cc. of blood.

Ito [cit. Uchida (3534)] reported that from his observations and according to dermatological statistics covering a period of 20 years, acetylsalicylic acid is responsible for 0.7 per cent of all drug eruptions.

In 1934 Lowy submitted questionnaires to 8,500 hospitals in the United States concerning cases of poisoning, "addiction," and death from barbiturates and antipyretics among admissions during a 10-year period. In 2,046 hospitals with a total annual admission of approximately 2½ million patients, 115 cases of "addiction," 74 cases of poisoning and 4 deaths were attributed to acetylsalicylic acid.

In 1940 the *Lancet* (3980) reported the occurrence in England and Wales of 33 fatalities due to acetylsalicylic acid in 1936, 61 in 1937, and 65 in 1938.

Varady and Jahn [1940] reported 45 cases of women hospitalized after suicidal attempts with acetylsalicylic acid. Seventeen of them who had taken 16 to 50 g. of acetylsalicylic acid developed marked decrease in the alkali reserve, and acetoneuria. The intraocular pressure was also markedly decreased but returned to normal with recovery from the poisoning.

Coombs, Warren and Higley [1944] studied 84 patients who had been given 10 to 16 g. of sodium salicylate a day. When the concentration of salicylate exceeded 30 mg. per 100 cc. of plasma they observed an alkalosis, decreased renal function, numbness and tingling of the extremities, pustular acne resembling that in bromism, and delirium.

Hopkins [1945] summarized the cause of deaths from acetylsalicylic acid in England and Wales for the years 1938 to 1942 as recorded by the Registrar General. His findings are shown in Table 19.

Manchester [1946] treated 54 young rheumatic patients with sodium salicylate intravenously and with sodium salicylate or acetylsalicylic acid orally. Mild reactions such as nausea, transient vomiting, deafness, tinnitus, vertigo and sweating were ignored as insignificant. The frequency of symptoms sufficiently severe to require interruption of the therapy with intravenous injection and oral administration, respectively, was as follows: delirium, 17 and 0 per cent; accentuation of dyspnea or signs of cardiac failure, 6 and

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TABLE 19.—Deaths from Acetylsalicylic Acid in England and Wales, 1938-42*

Year†	SUICIDES		ACCIDENTS		REASON UNDETERMINED	
	Males	Females	Males	Females	Males	Females
1938	18	25	3	5	5	9
1939	13	23	2	5	3	1
1940	14	32	5	7	0	0
1941	15	30	6	6	0	0
1942	8	27	5	5	0	0
Totals	68	137	21	28	8	10

Totals

*Data of Hopkins (1662).

†Data for 1940-42 refer to civilians only.

3 per cent; severe dyspnea, 3 and 14 per cent; excessive vomiting, 3 and 0 per cent; renal pain, 3 and 0 per cent; skin eruptions, 3 and 0 per cent. Except for dyspnea all of the symptoms of poisoning occurred most often after intravenous therapy. Manchester attributed this fact to the abrupt and comparatively high rise in the concentration of salicylate in the blood associated with intravenous injection.

Storm van Leeuwen [1928] examined 100 individuals with asthma for hypersensitivity to acetylsalicylic acid and in 16 found that severe attacks of asthma were precipitated by this drug. Attempts at desensitization were mostly unsuccessful and usually dangerous.

Gardner and Blanton [1940] studied the frequency of idiosyncrasy to acetylsalicylic acid in allergic individuals. They reviewed the histories of 467 patients, all of whom suffered from some kind of allergy. In 5 cases acetylsalicylic acid may have been the allergen. In questioning 47 allergic patients who had taken acetylsalicylic acid, no allergic symptoms were discovered. One hundred and three consecutive admissions to an immunology clinic were given 5 gr. of acetylsalicylic acid. Only 2 patients felt a slight and transitory constriction in the chest. None of the patients reacted violently. Questionnaires were sent to 95 allergists concerning the frequency of sensitivity to acetylsalicylic acid among allergic patients. Approximately 170 cases of sensitivity were reported in 90,000 patients. Gardner and Blanton estimated that the incidence of any sensitivity to acetylsalicylic acid in the general population is approximately 2 per 1,000, and that of these only a small proportion have severe reactions.

From the summary reports of poisonings, no estimation can be made of the number of instances of nonfatal poisoning which have occurred or the rate of death in such poisonings, since it is probable that there is considerable duplication of individual cases in the various reports. The heterogeneous nature of the data likewise precludes any statistical evaluation of the frequency of occurrence of the various toxic symptoms in salicylate poisoning and the relationship between this frequency and such factors as the size of the dose, age, and sex. Finally, instances of allergic responses to salicylate have frequently been indiscriminately included in the summary reports of salicylate poisonings.

REPORTS OF INDIVIDUAL CASES OF POISONING

In contrast to the summary reports, much information concerning the frequency of various symptoms and the relation between dosage and severity of the poisoning may be obtained from individual cases as reported in the literature. Five hundred and seventy-nine such cases have been reported in sufficient detail to permit tabulation and summarization of pertinent data. Twenty-two of these cases have been eliminated here, however, because the facts as presented were inadequate to justify the statement that the symptoms were due to poisoning from salicylates.* Of the remaining 557 cases, 144 terminated fatally.†

The specific salicylates to which these 557 instances of poisoning were attributed are shown in Table 20. It will be seen that all but 75 of the nonallergic poisonings were due to sodium salicylate, acetylsalicylic acid and methyl salicylate. To simplify presentation in tabulations below, these 75 cases will be designated as due to "other salicylates." It will be seen also that 146 (83 per cent) of the poisonings attributed to an allergy are due to acetylsalicylic acid. As there was no reported difference in the allergic response to different salicylates all of these cases will be considered as a group.

*References to eliminated cases: 235, 958 (case 2), 1024, 1193 (case 2), 1314, 1318 (cases 1, 2, 3), 1371 (case 7), 1534, 1981 (cases 1, 2), 2372, 2610, 3137, 3140 (cases 1, 2), 3452, 3550, 3589 (case 2), 3868, 3936.

†After completion of this review a case of fatal poisoning by methyl salicylate in a 2-year-old boy was reported by Dooly and Coleman [1947]; two fatal cases, one in an adult and the other in a child, were reported by Krasnoff and Bernstein [1947]; and one fatal case has recently been reported by Cancelmo [1947].

TABLE 20.—*Number of Poisonings by Different Salicylates Reported in the Literature*

<i>Drug</i>	<i>Nonallergic</i>	<i>Allergic</i>	<i>Total</i>
Salicylic acid	32	9	41
Sodium salicylate	147	10	157
Acetylsalicylic acid	88	146	234
Methyl salicylate	72	1	73
Phenyl salicylate	9	4	13
Antipyrine salicylate	5	1	6
Methoxymethyl salicylate	5	0	5
Salicylsalicylic acid	2	0	2
Salicin	1	0	1
Cinchonidine salicylate	0	1	1
Mixtures of salicylates	14	3	17
Not stated	7	0	7
Totals	382	175	557

Table 21 presents the reasons for which the various salicylates were taken in 398 cases of poisoning in which this information was available. The frequent use of sodium salicylate in the treatment of rheumatic fever and the infrequent use of this drug as a home remedy would account for the relatively high incidence of poisonings in rheumatic fever therapy and the low incidence of accidental poisoning and suicidal attempts.

On the other hand, the extensive home use and hence availability of acetylsalicylate accounts for the predominance of suicidal attempts with this drug. The small number of accidental poisonings by acetylsalicylic acid suggests a relatively low toxicity for the amounts of this compound generally taken intentionally.

For methyl salicylate, the predominant number of poisonings

TABLE 21.—*Reasons for Administration as Reported in Poisoning by Salicylates*

<i>Reason for Medication</i>	<i>Nonallergic Poisoning</i>								<i>Allergic Poisoning</i>	
	<i>Sodium Salicylate</i>		<i>Acetylsalicylic Acid</i>		<i>Methyl Salicylate</i>		<i>Other Salicylates</i>		<i>All Salicylates</i>	
	No.	%	No.	%	No.	%	No.	%	No.	%
Rheumatic fever	113	81.9	16	22.2	1	2.3	32	54.2	20	23.5
Analgesia	3	2.2	17	23.6	1	2.3	3	5.1	36	42.4
Other medicinal use	15	10.9	10	13.9	10	22.7	22	37.3	28	32.9
Accidents	6	4.3	5	7.0	28	63.6	1	1.7	1	1.2
Suicidal attempts	1	0.7	24	33.3	4	9.1	1	1.7	0	0
Totals, reason stated	138	100.0	72	100.0	44	100.0	59	100.0	85	100.0
Reason not stated	9		16		28		16		90	
Totals, all cases	147		88		72		75		175	

was due to accidents. The medicinal use of methyl salicylate is mainly in external application. Although two instances of fatal poisoning were reported as due to absorption of the drug through the skin, most of the poisonings were due to swallowing of the drug for nonmedical reasons. As previously pointed out, the data of the U. S. Bureau of the Census indicate that about two-thirds of all poisonings with methyl salicylate occur in children under 5 years of age. Its attractive odor is the common inducement to swallowing it. In adult poisonings, methyl salicylate has often been taken in intoxicating beverages and in five of the cases reviewed here, three of them fatal, methyl salicylate was so used.

Table 22 shows the frequency of poisoning at various doses of salicylate. In the tabulation an arbitrary division in dosage was made as "up to 1.5 g.," which covers the amount most commonly taken for analgesia; "1.5 to 12 g.," the ordinary range of salicylate medication, particularly in the treatment of rheumatic fever; and "over 12 g.," which may be considered as a toxic amount often taken with suicidal intent.

The majority of poisonings with sodium salicylate occurred in doses of 1.5 to 12.0 g. and in the treatment of rheumatic fever. The largest number of poisonings with acetylsalicylic acid occurred after taking toxic doses of over 12 g. This is in keeping with the fact that the greatest number of acetylsalicylic acid poisonings was due to suicidal attempts. With methyl salicylate, the majority of poisonings was also in this dose range and it was consumed for the most part accidentally. Since in individuals allergic or hypersensitive to a drug the dose of the drug taken is of minor significance, three-fourths of the allergic poisonings with salicylate occur with doses of 1.5 g. or under.

TABLE 22.—*Doses of Salicylates as Reported in Cases of Poisoning*

Doses Used*	Nonallergic Poisoning								Allergic Poisoning	
	Sodium Salicylate		Acetylsalicylic Acid		Methyl Salicylate		Other Salicylates		All Salicylates	
	No.	%	No.	%	No.	%	No.	%	No.	%
Up to 1.5 g.	0	0	14	19.7	0	0	13	23.6	73	75.3
1.5-12 g.	98	77.8	19	26.8	5	10.9	37	67.3	24	24.7
Over 12 g.	28	22.2	38	53.5	41	89.1	5	9.1	0	0
Total, dose stated	126	100.0	71	100.0	46	100.0	55	100.0	97	100.0
Dose not stated	21		17		26		20		78	
Total, all cases	147		88		72		75		175	

*Expressed in salicylic acid equivalent.

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In Table 23 the incidence of salicylate poisonings is shown by selected age classes. A considerable part of the poisonings from sodium salicylate, in proportion to population, occurs in the age class 5-14 years; this represents the period with highest frequency of onset of rheumatic fever. The highest incidence of poisonings by acetylsalicylic acid occurred in the age class 15-60 years. The probable explanation for this is that suicidal attempts, which occur predominantly in those over 15, are the cause of one-third of the poisonings by acetylsalicylic acid. Half of the cases of methyl salicylate poisoning tabulated here occurred in the age class 1-4 years. The predominance of accidental methyl salicylate poisoning in children and its reasons have been discussed previously. The large number of methyl salicylate poisonings occurring in the age class 15-60 years may be explained by the use of this drug as an intoxicant in beverages.

TABLE 23.—*Age of Individuals Poisoned by Salicylates*

Age Class	Poisoned by Salicylates									
	Sodium Salicylate		Nonallergic Poisoning				Allergic Poisoning		All	
	No	%	Acetylsalicylic Acid	Methyl Salicylate	Other Salicylates	No.	%	No.	%	
Under 1 yr.	0	0	4	5.2	5	7.5	8	12.3	2	2.2
1-4 yrs.	4	3.4	8	10.4	33	49.2	8	12.3	0	0
5-14 yrs.	31	26.3	6	7.3	3	4.5	12	18.5	1	1.1
15-60 yrs.	81	68.6	54	70.1	26	38.8	36	55.4	35	91.4
Over 60 yrs.	2	1.7	5	6.5	0	0	1	1.5	3	3.3
Total, age stated	118	100.0	77	100.0	67	100.0	65	100.0	91	100.0
Age not stated	29		11		5		10		84	
Total, all cases	147		88		72		75		174	

The data in Table 23 show that poisoning occurs almost exclusively in children.

The data in Table 23 show that allergic poisoning by salicylate occurs almost exclusively in adults. The data on allergic poisonings in this table, however, are for all salicylates combined and the question arises whether these age-class incidences may not be a factor of the differences in the particular salicylate compounds predominantly used by each group. This point is clarified by a comparison of the number of allergic and nonallergic poisonings due to acetylsalicylic acid alone occurring in nine age classes as shown in Figure 20. Below age 15 there are no instances of allergic poisoning attributed to acetylsalicylic acid.

Table 24 shows the frequency of poisonings in relation to the period over which salicylates were taken. The highest percentage of poisonings for the different compounds occurs after periods of

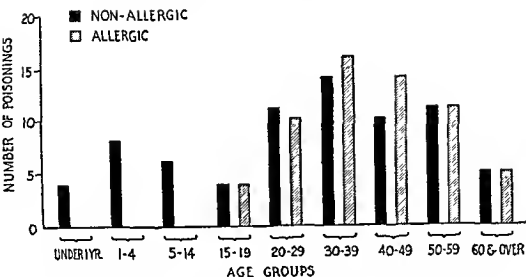


FIGURE 20.—Number of allergic and nonallergic poisonings attributed to acetylsalicylic acid in various age groups.

intake which are explainable by the data presented in Tables 21 and 22 concerning the relation of frequency of poisoning to dosage and reason for drug intake. The greatest number of sodium salicylate poisonings occurs during the first week of medication. The greatest percentage of such cases also occurs in the treatment of rheumatic fever in which large doses are administered daily, resulting in a gradual building up of the concentration of salicylate in the blood.

The maximum percentage of acetylsalicylic acid poisonings occurs

TABLE 24.—*Period over which Salicylates were Taken in Cases of Poisoning*

Duration of Intake	Nonallergic Poisoning								Allergic Poisoning All Salicylates	
	Sodium Salicylate		Acetylsalicylic Acid		Methyl Salicylate		Other Salicylates		No.	%
	No.	%	No.	%	No.	%	No.	%		
Single dose	3	2.7	16	25.8	55	85.9	4	7.8	46	54.7
Up to 1 day	23	20.5	22	35.5	6	9.4	18	35.3	15	17.8
Up to 1 week	59	52.7	12	19.4	2	3.1	19	37.3	14	16.7
Up to 1 month	19	17.0	3	4.8	1	1.6	7	13.7	3	3.6
Up to 1 year	8	7.1	2	3.2	0	0	2	3.9	4	4.8
More than 1 year	0	0	4	6.5	0	0	1	2.0	1	1.2
Chronic intake of unknown duration	0	0	3	4.8	0	0	0	0	1	1.2
Total, duration stated	112	100.0	62	100.0	64	100.0	51	100.0	84	100.0
Duration not stated	35		26		8		24		91	
Total, all cases	147		88		72		75		175	

with a drug intake of one day, since a large percentage of these poisonings was due to suicidal attempts using massive doses of the drug. Most of the poisonings from methyl salicylate occur after a single large dose, for in most instances its ingestion was accidental. The occurrence of most allergic poisonings after a single small dose of salicylate is attributable to the relative unimportance of the quantity of salicylate taken where hypersensitivity is involved.

The degrees of poisoning, classified as slight, medium, severe or fatal, due to the different salicylate compounds, are shown in Table 25. With methyl salicylate almost two-thirds of the poisonings were fatal and few were slight. In the nonallergic poisonings with acetylsalicylic acid, half of those reported were severe or fatal; one-third were fatal. At the other extreme, nearly half of the allergic poisonings were slight and only about 5 per cent were fatal.

TABLE 25.—*Severity of Poisoning by Salicylates*

Degree of Poisoning	Nonallergic Poisoning								Allergic Poisoning All	
	Sodium Salicylate		Acetylsalicylic Acid		Methyl Salicylate		Other Salicylates		Salicylates	
	No.	%	No.	%	No.	%	No.	%	No.	%
Slight	30	20.4	18	20.5	4	5.6	25	33.3	82	46.8
Medium	46	31.3	22	25.0	9	12.5	17	22.7	75	42.9
Severe	31	21.1	17	19.3	14	19.4	13	17.3	10	5.7
Fatal	40	27.2	31	35.2	45	62.5	20	26.7	8	4.6
Totals	147	100.0	88	100.0	72	100.0	75	100.0	175	100.0

Table 26 presents the sex distribution in poisoning by salicylates. With sodium salicylate and acetylsalicylic acid, the distribution is equal between the sexes. With methyl salicylate, two-thirds of the poisonings occurred in males. From a tabulation of the sex and age distribution in poisoning by methyl salicylate (Table 27), it will be seen that a high ratio of male to female poisonings occurs in children in the age class 1-5 years and again in the adult group.

TABLE 26.—*Sex Distribution in Poisoning by Salicylates*

Sex	Nonallergic Poisoning								Allergic Poisoning All	
	Sodium Salicylate		Acetylsalicylic Acid		Methyl Salicylate		Other Salicylates		Salicylates	
	No.	%	No.	%	No.	%	No.	%	No.	%
Male	53	52.0	36	52.2	38	67.9	25	49.0	60	63.8
Female	49	48.0	33	47.8	18	32.1	26	51.0	34	36.2
Total, sex reported	102	100.0	69	100.0	56	100.0	51	100.0	94	100.0
Sex not reported	45		19		16		24		81	
Total, all cases	147		88		72		75		175	

TABLE 27.—*Sex and Age Distribution in Poisoning by Methyl Salicylate. (Individual Cases Collected from Literature.)*

<i>Age Class</i>	<i>Male</i>	<i>Female</i>	<i>Sex Not Reported</i>
Under 1 yr.	1	1	3
1-4 yrs.	17	8	8
5-14 yrs.	1	1	1
15-60 yrs.	16	6	4
Over 60 yrs.	0	0	0
Not reported	3	2	0
Total	38	18	16

The striking predominance of allergic poisoning in males suggests that either hypersusceptibility to salicylate is more frequent in men than in women or that salicylate in small amounts is taken by more men than women.

The frequency of various symptoms reported for nonallergic

TABLE 28.—*Frequency of Symptoms Reported in Nonallergic Poisoning by Salicylates*

<i>Symptoms</i>	<i>Sodium Salicylate (per cent)</i>	<i>Acetylsalicylic Acid (per cent)</i>	<i>Methyl Salicylate (per cent)</i>	<i>Other Salicylates (per cent)</i>
Collapse, unconsciousness, coma	26.5	36.4	34.7	34.7
Hallucinations, delirium	33.3	17.0	16.7	29.4
Neurological symptoms	15.0	17.0	12.5	8.0
Convulsions, spasms, tetany	7.5	18.2	38.9	17.3
Circulatory symptoms	27.2	28.4	40.3	24.0
Hyperventilation	36.7	35.2	66.7	38.7
Other respiratory symptoms	1.4	6.8	12.5	5.3
Vertigo	4.8	8.0	11.1	5.3
Gastrointestinal symptoms	29.9	42.0	69.5	25.3
Symptoms from liver and spleen	4.8	9.1	9.7	6.7
Headache	7.5	10.2	5.6	6.7
Kidney symptoms	18.4	20.5	30.6	14.7
Aural symptoms	33.3	21.6	25.0	22.7
Ocular symptoms	6.8	3.4	5.6	5.3
Effect on red blood cells	2.7	6.8	2.8	1.3
Effect on white blood cells	1.4	10.2	9.7	4.0
Disturbance of acid-base equilibrium	49.0	36.4	68.1	42.7
Acetone or ketone bodies in blood, urine or breath	14.3	12.5	27.8	16.0
Glycosuria or effect on glycemia	4.8	4.5	9.7	4.0
Hemorrhage	18.4	27.3	19.4	12.0
Hypoprothrombinemia	8.2	0	0	0
Fever	14.3	15.9	34.7	20.0
Other symptoms	17.0	23.9	19.4	4.0

TABLE 29.—*Frequency of Symptoms Reported in Allergic Poisoning by Salicylates*

<i>Symptoms</i>	<i>Number of Cases Per Cent</i>	
Asthma alone	49	28.0
Edema and skin eruption	44	25.1
Skin eruption alone	40	22.9
Other allergic symptoms alone	12	6.9
Edema alone	9	5.1
Asthma and other allergic symptoms	5	2.9
Skin eruption and other allergic symptoms	5	2.9
Edema, skin eruption and other allergic symptoms	4	2.3
Edema and other allergic symptoms	4	2.3
Asthma, skin eruption and other allergic symptoms	1	0.6
Edema and asthma	1	0.6
Skin eruption and asthma	1	0.6
Total with		
Skin eruption	95	54.6
Edema	62	35.6
Asthma	57	32.6
Other allergic symptoms	31	17.8

poisoning by salicylate is shown in Table 28. In evaluating the data in this table it must be borne in mind that many of the more serious symptoms would mask or exclude less severe ones. Thus, in collapse, unconsciousness or coma, such minor symptoms as vertigo or aural symptoms would not be apparent and would not be reported. The data in Table 28 yield information on the kind but not on the incidence of the less severe symptoms in mild or moderate poisoning. Further symptoms that depend for their detection on laboratory determination, such as hypoprothrombinemia, are limited less by their occurrence than by the investigations for them.

Table 29 shows the frequency of various symptoms in allergic poisonings by salicylates. Dermal symptoms occur in more than half. The symptoms ordinarily observed in nonallergic poisonings were rare. The "other allergic symptoms" referred to in this table are, in decreasing order of their frequency: vasomotor rhinitis, choking, unconsciousness and collapse, abdominal cramps, perspiration, precordial pain, cyanosis, low blood pressure, headache, salivation, vertigo, shock, blurred vision, chills, palpitation, pulmonary edema, syncope, and sneezing.

CASE REPORTS OF FATAL POISONING

The data tabulated and summarized in the preceding sections included findings reported in 144 cases of fatal poisoning. There were in addition 14 cases in which there is considerable doubt that

salicylate was the actual cause of death. These 14 cases are part of the group of 22 cases, fatal and nonfatal, excluded from the statistical analysis as noted previously (see p. 161). In the present section a history is given of each reported fatal salicylate poisoning, and the 14 questionable cases are included and identified by an asterisk at the beginning of each such case report. Each case report in this section includes a description of the symptoms together with as much pertinent detail as can be obtained from the reports in the literature, and the autopsy findings when reported. Many of the fatalities occurred in ill or debilitated individuals and many of the symptoms and findings described are undoubtedly due to the underlying disease rather than to salicylate.

Salicylic Acid

ABELIN [1877]

A baby, age 4 months, was given 0.8 to 1.0 g. of salicylic acid. Symptoms included irritation of mouth and pharynx, irregular respiration, albuminuria, casts in urine and collapse. The baby died with pneumonia on the tenth day. Autopsy showed enlargement of the kidneys with hemorrhages.

EMPIS [1877]

*A woman, age 46, suffering from rheumatic fever, received 7 g. of salicylic acid on the seventh day of illness and 5 g. on the eighth day. The following day she was relieved of pains and fever, but was weak, perspired, and complained of tinnitus and deafness. During the following night, shortly after she had asked for and eaten a small meal, she had a convulsive seizure and died. The usual symptoms of severe salicylate intoxication were missing, and the patient was conscious until the seizure started. Empis did not attribute her death to a direct action of salicylic acid.

SÉE [1877 (3140)]

*Two cases are mentioned briefly, one in Russia where 18 g. of salicylic acid was fatal and one in Germany, where 12 g. was fatal.

STRICKER, cit. ROVIRA [1878]

An adult male with acute rheumatic fever took 3 g. of salicylic acid in divided doses. Symptoms included headache, vomiting and loss of consciousness. Death occurred 40 hours after the first dose.

GOODHART [1880]

*Three cases are reported of sudden death in young women after ingestion of salicylic acid (amounts not stated), but with no changes in the viscera sufficient to cause death.

KÜSTER [1882]

*A woman in poor general condition was operated on for a purulent parametric infection. The wound was filled with salicylic acid. The next day she had an accelerated pulse and collapsed, dying 1 day later.

*An aged man underwent surgery for sarcoma of the skin. The wound was filled with salicylic acid. There was bleeding that evening, fever, collapse and death the next day.

A woman, age 27, was operated on for hydronephrosis. A large amount of salicylic acid was placed deep into the wound. The next day she was unconscious and cyanotic; her pupils were dilated and did not react to light; she had continuous clonic convulsions. Death occurred 24 hours after the operation.

ESCHERICH, cit. FEER [1904]

A boy, age 2, had an itching dermatitis to which salicylic acid was applied. The next morning he was unconscious, cyanotic and dyspneic and died from cardiac failure. Autopsy findings showed lymphatism and fatty degeneration of the liver.

WYSS, cit. FEER [1904]

Salicylic acid in olive oil was accidentally applied three times in 16 hours to the skin of an infant, age 1½, with eczema. Dyspnea, cyanosis, apathy, jerking of arms and legs, and finally death occurred. Autopsy findings showed a large thymus, epicardial hemorrhages, congestion and edema of lungs, and enlargement of spleen.

LENARTOWICZ [1914]

A patient, age 16, with lupus vulgaris, tuberculosis of the foot and otitis media, used an ointment containing salicylic acid on the entire leg. Vomiting, tinnitus, headache, stupor, Cheyne-Stokes breathing, and rigidity of head and neck followed. Death occurred the next day. Autopsy showed persistent hyperplastic thymus, pericardial ecchymoses, myocardial degeneration and edema of various organs.

ZUMEROICH [1918]

A child, age 13 months, had been given applications of salicyl-vaseline on the head for eczema. Dyspnea and convulsions developed. Autopsy showed hyperemia of the lungs and brain, ecchymoses of the pleurae, and fatty degeneration of the kidneys.

KIESS [1921]

Two boys, age 5 and 7, were given salicyl-tar dressings (6 per cent salicylic acid and 15 per cent juniper tar in alcohol) for scabies, pediculosis and eczema. Vomiting, thirst, sudden collapse, slow reaction of pupils, and dyspnea followed. Death occurred on the second day. Autopsy showed fatty infiltration of the liver in the younger boy; and bronchopneumonia, tuberculosis of the lymph glands and severe fatty infiltration of the liver in the older boy.

KALBE [1923]

Two boys, age 5 and 6, were given over the whole body three applications containing salicylic acid for scabies. Vomiting, intense thirst, cardiac weakness and incontinence followed. In the younger boy, death occurred 36 hours after the first application, and in the older one, a day later. Autopsy showed fatty infiltration of the liver and spleen.

Sodium Salicylate

GOLTDAMMER [1876 (1314)]

*In a talk given before a medical society at Berlin, the case was mentioned of a patient with typhoid who was given 5 g. of sodium salicylate in the fifth week of illness. The temperature was reduced to 35.2° C. The patient collapsed and died.

DUJARDIN-BEAUMETZ [1877]

A man, age 33, took about 45 g. of sodium salicylate in 5 days for acute rheumatic arthritis. The symptoms mentioned were gangrene of the right foot and leg, hematuria, hemoptysis, constipation and excitement. He died on the ninth day.

JACCOUD, cit. OULMONT [1877]

A man, age 23, an alcoholic, received 10 g. of sodium salicylate for rheumatic fever. After 48 hours, he developed an endocarditis and pericarditis; the next day he was delirious. He died on the ninth day.

A man, age 23, received 10, 12 and 6 g. of sodium salicylate on the sixth, seventh and eighth days of rheumatic fever, respectively. He died on the ninth day with symptoms of acute encephalopathy.

A man, age 20, began sodium salicylate medication on the eighth day after the onset of acute rheumatic fever, and died 3 days later. Death was preceded by violent delirium and coma.

QUINCKE [1882]

A girl, age 17, with chronic articular rheumatism, received first 10, then 12 g. of sodium salicylate daily. Symptoms after the third day included tinnitus, dizziness, nausea, dyspnea, then stupor and coma. Autopsy revealed severe hyperemia of the brain, and chemical analysis showed the presence of salicylic acid in various organs.

OOSTON [1883]

*A man, age 29, diagnosed as rheumatic, took 1 g. of sodium salicylate after having pains in the right side. He slept, became drowsy, and was comatose 8 hours later. His breathing was slow and stertorous, his temperature normal. The extremities were cold, and the face, neck and ears had a purple tinge. He died 16½ hours after taking the salicylate. On autopsy it was found that surface vessels of the brain were engorged, the right heart was distended, and the lungs, containing no air, were filled with dark, clotted blood. In the left lung there was a small, partly cheesy and chalky knot, and in the right, a cartilaginous cicatrix. There were punctate ecchymoses over the entire surface of the stomach mucosa.

WHIPHAM [1888]

A man, age 47, was given potassium bicarbonate, "iod. sod. salicyl.," quinine and opium for rheumatic fever. The only symptom mentioned was hyperpyrexia. Death occurred on the nineteenth day.

A man, age 27, was given 15 gr. of sodium salicylate every 4 hours for rheumatic fever. Only hyperpyrexia was mentioned as a symptom. He died on the seventh day.

A man, age 35, was given for rheumatic fever 10 gr. of sodium salicylate every 2 hours, then 15 gr. with 30 gr. of sodium bicarbonate together with potassium iodide and colchicum, quinine and brandy. On the twenty-first day he had hyperpyrexia. He died on the twenty-third day.

VON ACKEREN [1890]

A patient took 12 g. of sodium salicylate in 3 days as an antipyretic. He developed albuminuria and died on the fourth day. Autopsy showed nephritis and caseous foci in the kidneys.

MEHRER [1893]

*A man, age 40, was given 18 g. of sodium salicylate in 3 days for exudative

HALLÉ, cit. PAISSEAU, FRIEDMAN and VAILLE [1934 (2659)]

An old woman was found unconscious, breathing very slowly, and with an empty bottle originally containing 35 g. of sodium salicylate. She was thought to have taken the contents of the bottle. She died after 2 days.

MADISON [1934]

A young man, age 18, was given 50 g. of sodium salicylate during 3 days for acute articular rheumatism. Vomiting, tinnitus, agitation, deep rapid breathing and unconsciousness followed. Autopsy showed pericarditis, endocarditis and perihepatitis, subperitoneal, subpleural and renal ecchymoses, and subdural hemorrhage.

A woman, age 39, with acute articular rheumatism, was given 15 g. of sodium salicylate intravenously and 17.25 g. of salicylsalicylic acid during a period of 6 days. Nausea, tinnitus and cardiac weakness followed. Autopsy showed myocardial, renal and hepatic degeneration, endometritis, pleurisy, and hemorrhages in the pericardium, pleurae, dura mater and peritoneum.

NAVARRO and HUERGO [1934]

A boy, age 11, with rheumatic fever, had tolerated high doses of sodium salicylate for months. Abruptly toxic symptoms developed, with dyspnea, delirium, stupor, diuresis, albuminuria, enlargement of the liver, anasarca and finally tachycardia, arrhythmia, coma and death.

PAISSEAU, FRIEDMAN and VAILLE [1934 (2659)]

A girl, age 10, was given large doses of sodium salicylate with sodium bicarbonate for rheumatic fever. Vomiting, drowsiness, Kussmaul breathing, acidosis (urinary pH 5.0, presence of ketone bodies), exanthema, cyanosis, delirium, convulsions and coma followed. Autopsy showed hemorrhages of the pericardium, kidneys and brain, congestion of the lungs, brain and kidneys, and fatty degeneration of the liver and adrenals.

STRAUSS, ROSENTHAL and NOCERO [1934]

A man, age 40, with rheumatic fever, was given 260 gr. of sodium salicylate orally and by enema during 2 days, and methyl salicylate was applied to the joints. On the third day nausea, tinnitus, aphonia, prostration and coma developed and were quickly followed by death. Autopsy showed subserous hemorrhages of the lungs, heart and kidneys, hemorrhage into the spleen, sub-endocardial hemorrhage, hemorrhagic gastritis and mild parenchymatous degeneration of the kidneys and liver.

HAIMOVICI [1935]

A girl, age 10, had been treated previously with sodium salicylate for rheumatic fever. On relapse she was given 10 g. of sodium salicylate with 20 g. of sodium bicarbonate daily. This was poorly tolerated and was replaced by 7 g. of sodium salicylate, partly intravenously and partly by enema, with 10 g. of sodium bicarbonate daily for 3 days. Vomiting, agitation alternating with prostration, delirium and Kussmaul breathing followed. The alkali reserve of the blood fell to 9 volumes per cent. The urine was acid (pH 4.5) and contained ketone bodies, albumin and casts. Later erythema, cyanosis, coma and convulsions developed. Autopsy showed hemorrhages of the pericardium, kidneys and brain, congestion of the lungs and brain, and fatty infiltration of the liver.

DOBBS and DE SARAM [1938]

A girl, age 8, with rheumatic fever, was given 20 gr. of sodium salicylate with bicarbonate daily. Beginning on the fifth day, auditory hallucinations,

restlessness, hyperpnea and coma developed. The erythrocyte count of the blood was 2,800,000 and the leucocytes 13,800. Death occurred in 6 days. Autopsy showed acute hemorrhagic encephalitis, hemorrhages of the endocardium, pericardium, transverse colon and omentum, and recent rheumatic infection of the heart.

ASHWORTH and McKEMIE [1944]

A young woman, age 20, with relapse of acute rheumatic fever, was given 10 g. of sodium salicylate daily by intravenous injection for 2 days and orally for another 5 days. She became irrational and developed tachypnea, hyperpnea, cyanosis and hematuria. The erythrocyte count of the blood was 3,650,000, the leucocytes 11,050, and the carbon dioxide combining power of the blood 46 volumes per cent. She died in coma on the eighth day. Autopsy showed diffuse hemorrhages in the lungs; petechial hemorrhages throughout the brain and in the peritoneum, mesentery, retroperitoneal tissues, pericardium, spinal cord, intestines, pancreas and skin; small subdural hemorrhage; early bronchopneumonia; and parenchymatous degeneration of the liver.

HARTMANN [1945]

An infant, age 20 months, swallowed at least fourteen 5-gr. tablets of sodium salicylate. Extreme hyperpnea, coma, convulsions, acidosis and ketosis developed, and death resulted.

RAPOPORT, NIXON and BARKER [1945]

A soldier, age 35, with either rheumatic fever or rheumatoid arthritis, was given an unstated amount of sodium salicylate for 3 days. After 2 days without medication, he received 80 gr. of sodium salicylate for 33 days. After another interruption of 13 days, 30 gr. of sodium salicylate with sodium bicarbonate were given daily for 10 days. He developed a toxic thrombocytopenic purpura which was considered due to salicylate as no other drug had been given. He had epistaxis, hematuria, hematemesis and ecchymoses in oral and conjunctival mucosae. Blood transfusions were given nearly every day and splenectomy was performed. He died 42 days after salicylate medication was discontinued. At autopsy hemorrhages and ecchymoses were found in the skin, oral and nasal mucosae, pericardium, pleurae, gastrointestinal tract and bladder; and hemorrhagic effusions in the peritoneum, pericardium and pleurae.

RYDER, SHAVER and FERRIS [1945]

A girl, age 16, with acute rheumatic fever, was given 15 g. of sodium salicylate in about 36 hours. Tinnitus, nausea and vomiting followed. The drug was discontinued for 15 hours and then 1 g. was given every 4 hours. On the sixth day, after 26 g. had been given, vomiting, rapid and labored breathing, twitching and stupor occurred. The carbon dioxide combining power of the blood fell to 16.4 volumes per cent. Death occurred 66 hours after the last medication. Autopsy showed pericarditis, and congestion, degeneration and hemorrhages in the brain.

STEVENS and KAPLAN [1945]

A boy, age 10, with acute severe generalized polyarthritis, was given 6 g. of sodium salicylate daily for 5 days, partly orally and partly intravenously. Irritability, mental confusion, vomiting and hyperpnea followed. The carbon dioxide combining power of the blood fell to 14 volumes per cent. Pulmonary edema developed and he was given sodium lactate intravenously. He died with signs of circulatory failure. The results of chemical analyses of the salicylate content of the blood, reported only after his death, showed the high

level of 100 mg. per 100 cc. Autopsy showed petechial hemorrhages, enlarged heart, acute active pancarditis, fluid in the pericardial and abdominal cavities, acute early bronchitis, pulmonary edema and congestion, blood-tinged exudation in the lungs and bronchi, perivascular hemorrhages, atelectatic foci in the lungs, and edema of the convoluted tubules of the kidneys.

TARAN, JACOBS and KRAUTMAN [1945]

Two children with acute rheumatic carditis were given sodium salicylate intravenously ($1\frac{1}{2}$ gr. per pound of body weight during 6 hours). The temperature dropped and there was apparent improvement but on the third day of treatment tachypnea developed and the prothrombin time was prolonged. "Both children died in heart failure, completely disoriented and with the symptom of respiratory distress predominating."

TROLL and MENTEN [1945]

A boy, age 11, developed rheumatic fever and was given sodium salicylate. During $5\frac{1}{2}$ months he was given a total of 100 g. and then during 3 months a total of 50 g. He developed pulmonary edema, cyanosis, pulmonary edema and enlargement of the liver and heart developed. Autopsy showed widespread petechial hemorrhages; pericarditis, myocarditis and endocarditis; pleurisy; congestion of the lungs, liver and spleen; fatty infiltration of the liver; massive renal hemorrhage; and acute lymphadenitis.

CLAUSEN and JAGER [1946]

In a case of fatal sodium salicylate poisoning with severe hypoprothrombinemia, autopsy revealed only a few insignificant hemorrhages in the serous membranes.

JAGER and ALWAY [1946]

A patient with recurrent acute rheumatic fever had an immediate recurrence of active infection after sodium salicylate medication was discontinued on the fifty-ninth day of treatment. "This patient died of salicylate intoxication 38 days after therapy was resumed."

A man, age 41, with a relapse of rheumatic fever, had, on examination, mitral stenosis and insufficiency, auricular fibrillation, moderate leucocytosis, and an elevated erythrocyte sedimentation rate. For 71 days he was given equal quantities of sodium bicarbonate and sodium salicylate in maximal daily oral dosage of 18 g. He developed pulmonary edema, and medication was discontinued for a week, after which it was resumed first with 0.14 g. per kg., later 0.23 g. per kg. Twenty-one days after resumption, the concentration of salicylate in the plasma was 43.2 mg. per 100 cc. Five days later the patient developed drowsiness, tinnitus, blurred vision and hyperventilation. The next day the concentration of salicylate in the plasma was 81.2 mg. per 100 cc. The plasma prothrombin time was greatly prolonged. He died 18 hours later in coma with marked cyanosis. Autopsy showed petechial hemorrhages in the epicardium, small intestine and brain. The lungs were edematous and congested, the brain edematous. The heart was enlarged, contained foci of lymphocytes and histiocytes, and was stenosed. Death appeared to be due to pulmonary edema.

Methyl Salicylate

JEWET [1868]

A man, age 55, took not more than $\frac{1}{2}$ oz. of oil of wintergreen after heavy drinking the previous day. He developed pain in the stomach and bowels,

labored respiration, vomiting, green vision and then loss of vision, and finally lapsed into coma.

ABLE [1885]

A man, age about 30, swallowed $\frac{1}{2}$ pint of oil of birch, which contains methyl salicylate. He appeared drunk and was nauseated and vomited; he then became semistuporous. Deafness and dyspnea were followed by coma.

HALDERMANN [1886]

A girl, age 2 years and 5 months, swallowed about 3 drachms of oil of wintergreen. This was followed during the next 18 hours by vomiting, restlessness, convulsions, coma and muscular rigidity.

PINKHAM [1887]

A young woman, 3 months pregnant, took 1 oz. of oil of gaultheria to induce abortion. She developed pain in the head, stomach and bowels, purging, diuresis, painful and involuntary micturation, blindness and deafness, spasms of the hands and feet, generalized convulsions, depression of heart action, and rapid respiration. Death occurred in 15 hours. Autopsy showed marked irritation of the gastrointestinal mucosa and congestion of the kidneys.

PILLSBURY [1900]

A middle-aged man ingested 2 oz. of oil of wintergreen. Diarrhea, gastric pain, rapid pulse, intense erythema and itching followed. Death occurred after 41 hours.

VAN WAGENEN [1900]

A boy, age 2, drank 1 teaspoonful of oil of wintergreen. Vomiting, delirium, hyperpnea and convulsions followed.

McNERTHNEY [1903]

A boy, age 3, swallowed 3 drachms of oil of wintergreen. After 3 hours he had severe epigastric pain, slight opisthotonos, twitching of limbs, dilated pupils, and slow and labored respiration.

PRICE and L'ENGLE [1904]

A child, age 2, drank about 1 drachm of commercial oil of wintergreen. Vomiting, hyperpnea, rapid pulse, deafness, visual hallucinations and convulsions followed. The child died about 10 hours after taking the drug.

LEGRAIN and BADONNEL, cit. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION [1922 (3915)]

A woman took 60 g. of methyl salicylate with suicidal intent. There were no immediate symptoms but within a few hours nausea, convulsions, semicoma and cyanosis occurred. She died in $5\frac{1}{4}$ hours.

HOWARD [1924]

A young man consumed about 6 cc. of methyl salicylate. He vomited, had convulsions, and died during the evening of the same day.

ARCHAMBAUD and FRIEDMANN [1926]

A girl, age 17, accidentally drank a liniment composed of 40 g. of methyl salicylate and 60 g. of Fioraventi balm. Vomiting, headache, nausea, dyspnea, coma and cyanosis occurred. She died in 34 hours.

WETZEL and NOURSE [1926]

An infant, age about 21 months, drank about 10 cc. of oil of wintergreen. Vomiting, cyanosis, rapid and deep respiration, abnormal reaction of pupils

to light, and finally coma and pulmonary edema followed. Death occurred after 36 hours. Autopsy showed hemorrhages in the pleurae, lungs, heart (subepicardial), deep tissue over the occipital protuberance down to the epicranium, left frontal region, and beneath the dura over the entire left cerebral hemisphere.

ARNOLD and JACOBSEN [1927]

A boy, age 10 months, swallowed not more than 10 cc. of methyl salicylate. Two and one-half hours after ingestion, the physician noticed no signs of serious poisoning. Later vomiting, labored and rapid respiration, convulsions, stupor, a strong acetone reaction in the urine, and cyanosis developed. Death occurred in 16½ hours. Autopsy showed hemorrhages in the brain and liver, acute congestion of the lungs, spleen, liver and kidneys, fatty degeneration of the liver, degeneration of the heart and acute edema of the lungs.

PINCUS and HANDLEY [1927]

A boy, age 22 months, swallowed oil of wintergreen, not in excess of 60 cc. He vomited. Ten hours later his pulse was 164, respiration 36, temperature 99.6°. The heart, lungs, reflexes, vision and hearing were normal. One hour later he had convulsions and became cyanotic, with respiration (145 mg. per cent) and an increased nonpro (145 mg. per cent) were found. He died in 14 hours.

WOODBURY and NICHOLLS [1928]

A man, age 25, who had access to oil of wintergreen, was found dead with an odor of methyl salicylate in his room and about his body. Autopsy showed edema and congestion of the lungs and acute parenchymatous degeneration of the kidneys. The stomach contained some bloody fluid which gave a salicylate reaction. The urine contained no albumin or blood; its salicylate content was estimated as 0.5 g.

A boy, age about 22 months, swallowed an unknown quantity of oil of wintergreen. A few hours later he vomited and had convulsions. Tetany developed and lasted until death the next day. Autopsy showed congested areas in the gastric mucosa and congestion and engorgement of the lungs. The urine contained methyl salicylate.

PHARMACEUTICAL JOURNAL [1929 (4053)]

An instance of fatal poisoning is reported in which a man, age not recorded, drank an unknown amount of methyl salicylate accidentally.

BAUBY and FROMONT [1930]

A soldier took an unknown amount of methyl salicylate to simulate heart disease. (He was suspected of having done so several times previously.) Nausea, vomiting, dilated pupils, difficulty in walking and talking, dyspnea and coma occurred and were followed by death. Autopsy showed congestion of the lungs, stomach, liver and brain, fatty degeneration of the heart, and periglomerular inflammation of the kidneys. The kidneys, lungs, stomach, liver, intestines, bile and urine contained salicylic acid. Methyl alcohol and an ester of salicylic acid were found in the liver.

MEYERHOFF [1930]

A boy, age 22 months, swallowed about 24 cc. of methyl salicylate. He vomited continuously and was somewhat cyanotic. The next day his pupils were first contracted and later dilated and sluggish. The abdomen was dis-

labored respiration, vomiting, green vision and then loss of vision, and finally lapsed into coma.

ABLE [1885]

A man, age about 30, swallowed $\frac{1}{2}$ pint of oil of birch, which contains methyl salicylate. He appeared drunk and was nauseated and vomited; he then became semistuporous. Deafness and dyspnea were followed by coma.

HALDERMANN [1886]

A girl, age 2 years and 5 months, swallowed about 3 drachms of oil of wintergreen. This was followed during the next 18 hours by vomiting, restlessness, convulsions, coma and muscular rigidity.

PINKHAM [1887]

A young woman, 3 months pregnant, took 1 oz. of oil of gaultheria to induce abortion. She developed pain in the head, stomach and bowels, purging, diuresis, painful and involuntary micturation, blindness and deafness, spasms of the hands and feet, generalized convulsions, depression of heart action, and rapid respiration. Death occurred in 15 hours. Autopsy showed marked irritation of the gastrointestinal mucosa and congestion of the kidneys.

PILLSBURY [1900]

A middle-aged man ingested 2 oz. of oil of wintergreen. Diarrhea, gastric pain, rapid pulse, intense erythema and itching followed. Death occurred after 41 hours.

VAN WAGENEN [1900]

A boy, age 2, drank 1 teaspoonful of oil of wintergreen. Vomiting, delirium, hyperpnea and convulsions followed.

McNERTHNEY [1903]

A boy, age 3, swallowed 3 drachms of oil of wintergreen. After 3 hours he had severe epigastric pain, slight opisthotonos, twitching of limbs, dilated pupils, and slow and labored respiration.

PRICE and L'ENGLE [1904]

A child, age 2, drank about 1 drachm of commercial oil of wintergreen. Vomiting, hyperpnea, rapid pulse, deafness, visual hallucinations and convulsions followed. The child died about 10 hours after taking the drug.

LEGRAIN and BADONNEL, cit. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION [1922 (3915)]

A woman took 60 g. of methyl salicylate with suicidal intent. There were no immediate symptoms but within a few hours nausea, convulsions, semicoma and cyanosis occurred. She died in $5\frac{1}{4}$ hours.

HOWARD [1924]

A young man consumed about 6 cc. of methyl salicylate. He vomited, had convulsions, and died during the evening of the same day.

ARCHAMBAUD and FRIEDMANN [1926]

A girl, age 17, accidentally drank a liniment composed of 40 g. of methyl salicylate and 60 g. of Fioraventi balm. Vomiting, headache, nausea, dyspnea, coma and cyanosis occurred. She died in 34 hours.

WETZEL and NOURSE [1926]

An infant, age about 21 months, drank about 10 cc. of oil of wintergreen. Vomiting, cyanosis, rapid and deep respiration, abnormal reaction of pupils

DUVOIR, POLLET and SAINTON [1934]

A man, age 34, an alcoholic, took about 200 cc. of methyl salicylate for suicide. Vomiting, restlessness, dyspnea, delirium and hallucinations followed. Death occurred in 36 hours. Autopsy showed congestion and edema of the lungs, blood in the stomach, localized fatty degeneration of the liver, congestion of the kidneys, and slight spotty hemorrhages of the brain.

ARNOLD, cit. LINDSAY [1937]

An infant, age 9 months, was given a small amount of oil of wintergreen. There were no symptoms at first, but the child died after a few days.

BEAVEN, cit. LINDSAY [1937]

Oil of wintergreen was applied to the joints of a girl with rheumatism. Hyperpnea and fever followed, and death in 48 hours. The findings at autopsy were reported as typical of salicylate poisoning.

LAWSON and KAISER [1937]

A man, age 26, used 10 to 12 oz. of methyl salicylate as a liniment over a period of weeks. Delirium, convulsions and coma followed, and the carbon dioxide combining power of the blood fell to 31 volumes per cent. He died of pancarditis.

STEVENSON [1937]

A girl, age 1 month, was given 5 cc. of oil of wintergreen. Vomiting, Kussmaul breathing, rapid pulse and coma followed. The carbon dioxide of the blood was 41 volumes per cent. Death occurred in 23½ hours. Autopsy showed subpleural and subepicardial hemorrhages.

BAXTER, HARTWELL and RECK [1938]

A child, age 3, swallowed 60 cc. of oil of wintergreen. Vomiting, hyperpnea, dehydration, drowsiness and cyanosis followed. The leucocyte count rose to 20,500. Death occurred in 22 hours. Autopsy showed petechial hemorrhages in the visceral pleurae, endocardium, pericardium, epicardial surface of the heart, and gastric and jejunal mucosae; bronchopneumonia with pulmonary edema; dilatation of the heart; hyperemia of the liver with parenchymatous degeneration; and degeneration of the tubular epithelium of the kidneys. Salicylate was present in the urine.

An infant, age 18 months, swallowed an unknown quantity of oil of wintergreen. Vomiting, convulsions, rapid and deep respiration, dehydration, cyanosis and coma followed. Death occurred in about 20 hours. Autopsy showed consolidation of most of the right lung and part of the left, with deep red, firm areas containing no air and with edema in the rest of the lungs; chronic passive congestion and parenchymatous degeneration of the kidneys and liver; and two shallow erosions, without hemorrhage, of the gastric mucosa. Methyl salicylate was present in the urine of the bladder.

EIMAS [1938]

A boy, age 22 months, swallowed one teaspoonful of oil of wintergreen. Vomiting, Kussmaul breathing, dehydration, drowsiness, cyanosis and convulsions followed. The leucocyte count was 18,500 and the carbon dioxide content of the blood, 57 volumes per cent. Death occurred in some 36 hours. Autopsy showed nephrosis, cloudy swelling and albuminous degeneration of the heart muscle, fatty degeneration of the liver, and pulmonary congestion and edema.

tended and tense; the reflexes were diminished. His temperature was 101° F., pulse 160 to 180, respirations 40 to 60, and he was dyspneic. He died the same day. Autopsy showed congestion of the lungs, kidneys and stomach, hyperplasia of the spleen and all lymphoid tissue of the intestinal tract, fatty degeneration of the liver, early glomerular nephritis, and terminal dilatation of the heart. The hemoglobin was reported as 63 per cent; erythrocytes, 4,900,000; leucocytes, 10,300, with 44 per cent neutrophils, 53 per cent lymphocytes, 2 per cent transitionals, and 1 per cent basophils. The feces were positive for bile. The fluid from colonic irrigation showed salicylate and blood; the urine obtained after death contained no salicylate.

HUGHES [1932]

A boy, age 17 months, was given 4 cc. of oil of wintergreen by accident. Dyspnea and coma followed, and death occurred in 12 hours. Autopsy showed erythema on the chest and abdomen, cyanosis of the legs and back, congestion of the lungs, abdominal viscera and kidneys, subpleural and subepicardial hemorrhages, atheroma-like degeneration of the mitral valve and at openings of vertebral arteries, early toxic changes in the liver, edema of the kidneys, and hyperemia of the brain and meninges.

LATHROP [1932]

A boy, age 19 months, swallowed an unknown amount of oil of wintergreen. Vomiting, dyspnea, cyanosis, convulsions and coma occurred. The carbon dioxide content of the blood was 33.2 volumes per cent. He died 19½ hours after ingestion of the drug. Autopsy showed hemorrhages of the epicardium, pleurae, pia and cerebellum, acute congestion of all organs, and degeneration of the kidneys with necrosis of the tubules.

PINCOFFS and CHAMBERS [1932]

A man, age 49, an alcoholic, took 1½ oz. of methyl salicylate during a drinking bout. He collapsed and for a time was unconscious. During the next 12 days he had vomiting, stupor, mental confusion, deafness, diminished reflexes, Kussmaul respiration, incontinence of urine, and delirium. An X-ray of the skull was negative. The hemoglobin was reported as 80 per cent; erythrocytes, 11,700. The urine contained albumin, sugar, blood urea was increased to 79 mg. per cc. on dioxide combining power of the plasma was as low as 28.8 volumes per cent. He developed pneumonia and died on the twelfth day.

A boy, age 21 months, swallowed an unknown amount of methyl salicylate. . . .
24 volumes per cent and the leucocyte count 23,850. Death occurred in about 21 hours.

VLEURINCK [1933]

An adult woman with chronic malaria committed suicide by a method used by women in southern Katanga and northern Rhodesia. She stuffed her vagina with the moistened bark of a root (lupapi or mweye) containing methyl salicylate. Weakness, bloody saliva and bloody vaginal discharge followed. She died in 6 days. Autopsy showed congestion of the minor curvature of the stomach, some exudate in the small pelvis, and hemorrhagic nephritis.

Abdominal cramps, vomiting, vertigo, tinnitus, agitation, dyspnea, cyanosis and convulsions followed. Two of the boys died in 36 hours. Autopsy showed congestion of the intestinal tract, lungs, and kidneys; subpericardial ecchymoses; enlargement of the liver and spleen; degeneration of the liver in one boy, and of the kidneys in both.

TROLL and MENTEN [1945]

A boy, age 2, swallowed about 30 cc. of oil of wintergreen. Vomiting, dyspnea, dehydration, cyanosis, enlargement of the liver, and convulsions followed. Death occurred in approximately 44 hours. Autopsy showed widespread petechial hemorrhages; enlargement of the thymus; enlargement of the lymph nodes; congestion of the viscera; fatty infiltration of the liver; and parenchymatous degeneration of the heart and kidneys.

LAFORET and COLLINS [1946]

A man, age 38, collapsed several hours after having swallowed, while in a state of alcoholic intoxication, not more than 24 cc. of a liniment which contained 20 per cent methyl salicylate. His temperature rose to 101° F. Reddish papules appeared on his face, and hyperactivity, dyspnea, vomiting, loss of consciousness, loss of pupillary light reflex, positive Babinski sign, cyanosis and convulsions followed. Death occurred in some 5½ hours.

Acetylsalicylic Acid

BULLETIN OF PHARMACY [1915 (3868)]

"A woman who had been sick for several days, and had been taking a mixture of quinine and acetylsalicylic acid regularly, died in convulsions. "That the mixture may have been the cause of her death seems quite plausible, especially in view of the fact that physicians . . . could find no evidence of other poison and decided that death was due to convulsions, the cause of which they were unable to learn."

LEWIS [1919]

A man, age 24, took nearly 200 gr. of acetylsalicylic acid in 6 hours for influenza. There was vomiting, anemia and passage of a large amount of blood in the feces, and unconsciousness. Death occurred the following day. Autopsy showed acute intestinal congestion and inflammation with hemorrhage.

HITCH [1928]

A man, age 31, with influenza, took 200 tablets of acetylsalicylic acid. Mental confusion, cutaneous hyperesthesia, cyanosis, dyspnea, involuntary evacuation of feces and urine, convulsions and coma followed. Autopsy showed gastric hemorrhage, congestion of the lungs, and edema of the lungs and meninges.

DE JANKOVICH [1928]

A man, age 26, committed suicide by taking 75 g. of acetylsalicylic acid in a liter of wine. He developed irregular pupils and diminished reflexes. Autopsy showed pleural and

A man, age 64, . . . acid for suicide. Vomiting, weakened reflexes : . . . Autopsy showed chronic inflammation of the kidneys; fatty degeneration of the kidneys and heart; and hemorrhages in the stomach and pericardium.

A woman, age 74, died the day after taking an unknown amount of acetylsalicylic acid with suicidal intent. Autopsy showed arteriosclerosis, aortic insufficiency, and small hemorrhagic spots in the gastric mucosa.

KANE [1938]

A girl, age 15 months, swallowed about 8 cc. of methyl salicylate. Convulsions and cyanosis followed. Gastric lavage resulted in a period of improvement, but symptoms soon recurred. Death resulted from respiratory and cardiac failure.

PHARMACEUTICAL JOURNAL [1940 (4055)]

The death of two infants, due to the accidental drinking of methyl salicylate, is reported without details.

SHIRREFF and PEARLMAN [1940]

A girl, age 15 months, swallowed an unknown quantity of oil of wintergreen. Vomiting, rapid breathing and acetonuria followed. After 19 hours her general condition improved but later cyanosis and convulsions developed. She died in 2 days.

A girl, age 32 months, swallowed not more than 8 cc. of oil of wintergreen. Vomiting, hyperpnea and difficulty in swallowing followed. She died in 25½ hours. Autopsy showed cyanosis; congestion of the liver, kidneys, ureters, lungs, brain and spleen; collapsed lungs; and subpleural and subpericardial hemorrhages. The carbon dioxide content of the heart blood at autopsy was 42 volumes per cent.

EPSTEIN and WORK [1942]

A boy, age 4, swallowed about 30 cc. of an oil of wintergreen rubbing mixture (methyl salicylate content not stated). He vomited and complained of abdominal pain and was admitted to a hospital where he was given sodium bicarbonate. After 5 hours his condition appeared normal and he was discharged. A few hours later, vomiting, restlessness, hyperpnea and abdominal pain developed. Thirteen and a half hours after taking the salicylate he became cyanotic, with difficult and rapid breathing (64 per minute). His pulse rate was 140 and his temperature 100.4°. His reflexes were normal. He was given caffeine, oxygen, saline and glucose, and 10 g. of sodium bicarbonate every 4 hours. There were general convulsions and twitchings. He died in 19 hours. Autopsy showed mild cyanosis; marked dehydration; edema and hyperemia of the brain; focal hemorrhages in the epicardium, lungs and gastric mucosa; mild edema and partial atelectasis of the lungs; and cloudy swelling of the kidneys.

SILVERMAN and PICCOLO [1942]

A boy, age 3, swallowed a small amount of oil of wintergreen. Vomiting, Kussmaul breathing, drowsiness, dehydration and hyperglycemia followed. He became cyanotic and developed convulsions.

MACCREADY [1943]

A child, age 3, swallowed about 7.5 cc. of methyl salicylate. Vomiting and convulsions occurred, and death in 2 hours.

TOWNSEND [1943]

A man, age 33, drank methyl salicylate liniment, not in excess of 4 oz. Vomiting, tinnitus, rapid and labored breathing, and collapse followed. After oral administration of liquids and sodium bicarbonate his condition improved. The leucocyte count fell to 2,400 and some crepitation was heard at the base of the lungs. He died in 24 hours.

DESROCHERS [1945]

Four boys, ages 16 to 18, drank a liquor containing methyl salicylate.

petence, congestion of the spleen and kidneys, and nephritis. Acetylsalicylic acid was found in the stomach.

EICHLER [1936]

A child, age 13½ months, was given 0.5 g. of acetylsalicylic acid on two successive days. On the third day, insomnia, weakness, cyanosis, dyspnea, stupor and hematuria developed and were quickly followed by death. Autopsy showed hemorrhages of the liver, lungs and heart, and edema of the brain.

NEALE [1936]

A man, age 45, mentally depressed, took an unknown amount of acetylsalicylic acid. Loss of memory, cyanosis, dyspnea, delirium and convulsions followed. Death occurred in about 12 hours.

A man, age 72, mentally depressed, took 150 tablets of acetylsalicylic acid with suicidal intent. He perspired profusely and died in approximately 12 hours.

A man, age 50, took 200 tablets of acetylsalicylic acid with suicidal intent. Coma developed and death occurred in about 12 hours.

A man, age 38, ordinarily took up to 30 gr. of acetylsalicylic acid to relieve the pain from tuberculosis of the hip. On taking 200 gr. in 36 hours, he vomited, became semiconscious, and died in 48 hours.

ORZECZOWSKI [1936]

A man, age 31, unstable mentally, took a large amount of acetylsalicylic acid. Staggering, vomiting and bewilderment followed. Autopsy showed ecchymoses in the brain. Large amounts of salicylate were found in various organs.

BIDDLE [1938]

A woman, age 30, with a history of dementia precox, swallowed about 400 gr. of acetylsalicylic acid within an hour. Restlessness, vomiting, insomnia, delirium, hyperpnea, convulsions and coma followed. Death occurred in 17 hours. Autopsy showed congestion of the brain and lungs, and edema and necrosis of the stomach.

FRIEDMAN [1938]

A man, age 25, was admitted to the hospital suffering from headache, vomiting, restlessness, cyanosis, irregular respiration, and rectus and facial palsy. He became comatose, and died 10 hours after admission. Autopsy showed gastric necrosis; hemorrhages in the spleen and brain; and congestion of the kidneys, liver, spleen and adrenals. Salicylate was found in the viscera.

*A woman, age 55, had been taking acetylsalicylic acid for 10 years for recurrent headaches. On the present occasion she took two tablets of a nostrum containing amidopyrine and a week later "much more than her usual dose of aspirin" for headaches of increased severity. Two days later she was seen by a physician who gave medication, but of unrecorded nature. She immediately vomited, and was unable to swallow. She developed moderate cyanosis, and shallow ulceration of the mucous membranes of the mouth, tongue, pharynx and vagina. Her pulse rate rose to 136. The leucocyte count was 700; granulocytes were absent. Autopsy showed focal necrosis of the liver; parenchymatous degeneration of the liver and kidneys; chronic rheumatic cardiovascular disease; fatty infiltration of the heart; fibromyoma of the uterus; fibroma of the kidneys; hypoplasia of the bone marrow; and hemorrhages and degenerative changes in the brain. The cause of death was given

A man, age 62, took about 21 g. of acetylsalicylic acid. Dizziness, headache, unconsciousness, convulsions and cyanosis followed. Autopsy showed dilatation of the heart; pulmonary stasis; and hemorrhages in the pericardium and endocardium.

A woman, age 34, took 20 g. of acetylsalicylic acid with suicidal intent. She vomited and was sent to a hospital. After gastric lavage, she was discharged. All that is known is that she perspired excessively and was found dead the next morning. Autopsy showed hemorrhages in the stomach, duodenum and endocardium.

HULTKVIST [1929]

A woman, age 31, took 50 g. of acetylsalicylic acid in about 5 hours for toothache. Precordial pain, convulsions and vomiting followed. Death by heart failure occurred less than 24 hours later. Autopsy showed induration of the spleen and dark brownish-purple discoloration of all muscles.

A mentally deranged man, age 55, took 50 g. of acetylsalicylic acid. Cyanosis, dyspnea, hallucinations, convulsions and coma followed. Death occurred in 8 hours. Autopsy showed coronary arteriosclerosis but no pathology attributable to salicylate was mentioned in the report.

PHARMACEUTICAL JOURNAL [1929 (4053)]

Two instances of fatal poisoning from acetylsalicylic acid are reported; the first, that of a man, age 40, who took a large amount with suicidal intent; and the second, that of an infant, age 3 months, who was given acetylsalicylic acid.

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION [1930 (50)]

Three women died during treatment of chronic arthritis with a preparation containing mainly acetylsalicylic acid and cinchophen. The principal autopsy findings were extensive atrophy of the liver. There were no findings typical of poisoning by salicylate.

BALÁZS [1932 (134)]

A woman, age 52, took 35 g. of acetylsalicylic acid with suicidal intent. Vomiting, dizziness, Kussmaul breathing, mental disturbance, acetonuria, cyanosis and convulsions followed. Autopsy findings showed ecchymoses in the stomach and hyperemia of the kidneys, lungs, liver, spleen and brain.

BALÁZS [1932 (135)]

A woman, age 28, took 120 5-gr. tablets of acetylsalicylic acid with suicidal intent. Kussmaul breathing, delirium, headache, tinnitus, acetonuria, cyanosis and convulsions developed. Death occurred in 48 hours. Autopsy showed edema of the stomach and intestines; hemorrhages in the stomach, small intestine, pleurae, and heart; parenchymatous degeneration of the kidneys; and anemic spots in the liver.

BALÁZS [1934]

A woman, age 30, attempted suicide with about 30 g. of acetylsalicylic acid. Vomiting, cyanosis, diminished reflexes, acetonuria, dyspnea, convulsions and coma followed. She died in 14 hours. Autopsy showed congestion of the pia mater, lungs, liver, spleen and kidneys and hemorrhage in the endocardium.

WYLLIE [1935]

A man, age 23, was found in coma shortly before he died. Autopsy showed persistent thymus, hemorrhages of the lungs and epicardium, mitral incom-

*Allergy***CHLAPOWSKI [1891]**

A woman was given 1 g. of salol in an Ewald test for gastric function. She became restless and lost consciousness. There were dilated pupils, heavy perspiration and an irregular pulse. Death occurred 12 days later. Autopsy showed gastritis and enteritis, gastric ulcer and chronic endometritis.

VANDER VEER [1920]

Following the ingestion of 5 g. of acetylsalicylic acid a patient immediately went into shock and died in 5 minutes.

WRIGHT [1930]

A woman, age 67, who had had asthmatic attacks for about 8 years, took 5 gr. of acetylsalicylic acid and $\frac{1}{4}$ gr. of codeine for "grippe." Three hours later the patient was cyanosed and gasping for breath. She was given 1 cc. of epinephrine. Her pulse, which had been 120, fell rapidly and she died. Autopsy showed thickening of the bronchi; the heart and vessels were normal. (Wright described this case under the title "Death from Bronchial Asthma" but MacDonald [1932] considered this a case of allergic reaction to acetylsalicylic acid.)

LAMSON and THOMAS [1932]

An asthmatic woman, age 54, who was hypersensitive to salicylate, took a preparation containing acetylsalicylic acid and caffeine. Acute allergic symptoms developed and she died in less than half an hour.

MACDONALD [1932]

A man, age 43, suffering from asthma for 5 years and hypersensitive to "coal-tar products," took 0.6 g. of acetylsalicylic acid. Half an hour later he had a severe attack of asthma and died. Autopsy showed only abnormality of the bronchi.

DYSART [1933]

An asthmatic woman, age 45, with a hypersensitivity to several foods, had twice previously shown severe reactions to acetylsalicylic acid. She took one tablet of acetylsalicylic acid for headache. The only symptom recorded was wheezing which grew progressively worse. Death occurred in 10 minutes. Autopsy showed a "normal heart, some tenacious mucus in the bronchi and a sarcoma of the dura, located over the left cerebral hemisphere."

FRANCIS, GHENT and BULLEN [1935]

An asthmatic man, age 27, had reacted twice previously to acetylsalicylic acid with severe asthma. After an attack of asthma, which had been relieved by ephedrine, epinephrine and barbiturate, he complained of headache and was given 10 gr. of acetylsalicylic acid. He collapsed and became unconscious and cyanotic, with a weak, thready pulse and a gasping respiration which later changed to an asthmatic type. He remained unconscious and died in 30 hours.

CALDER [1939]

A man was admitted to a hospital with acute bronchitis or possible bronchopneumonia. His general condition did not suggest that he was seriously ill. He reported that previously he had had violent asthma after acetylsalicylic acid. He complained of soreness and aching in the chest muscles but in spite of his statement a compound containing acetylsalicylic acid was prescribed. He died $1\frac{1}{2}$ hours later.

as agranulocytic angina. In view of the fact that amidopyrine and other drugs had been taken by this patient, death cannot be ascribed with certainty to acetylsalicylic acid.

HALSTRÖM and MÖLLER [1939]

A man, age 43, took an unknown amount of some salicylate, probably acetylsalicylic acid. Headache, weakness, insomnia, deafness, loss of memory, vomiting, rapid labored breathing, hypoglycemia, convulsions and coma followed. By chemical examination of all organs, a total of 18 to 20 g. of salicylic acid (equivalent of 23 to 26 g. of acetylsalicylic acid) was estimated to be present in the body.

SEARS [1939]

*A man, age 50, with tabes, had been taking 35 to 50 5-grain tablets of empirin daily for over 6 years. This dosage provided 120 to 175 gr. of acetylsalicylic acid, 80 to 125 gr. of phenacetin and 17 to 25 gr. of caffeine. Examination disclosed anasarca with prominent ascites, moderate anemia, and heart block. The empirin was prohibited but after a week the patient again took the preparation. Dyspnea followed and his pulse rate rose to 180. Death was attributed to extensive vascular degeneration and to heart block. No pathological findings could be traced to the excessive use of the components of the empirin compound.

BRITISH MEDICAL JOURNAL [1942 (3863)]

A woman, age 58, committed suicide by taking 90 tablets of acetylsalicylic acid.

HAWKINSON and KERR [1943]

A nurse, age 21, with a basal metabolism of -14, had taken thyroid and had lost 30 pounds. She had taken acetylsalicylic acid over a period of years, averaging 40 to 60 gr. a day. The erythrocyte count was 2,090,000, the leucocytes, 500. A diagnosis of agranulocytosis was made. Staphylococci were found in the blood. She developed a purpura and died. Autopsy showed bronchopneumonia; pleurisy; hypertrophy of the heart; subcutaneous, subepicardial, pericardial and renal hemorrhages; degeneration of the myocardium, liver and kidneys; congestion of the liver, kidneys and spleen; ulcer in the ileum but none in the pharynx; and hyperplasia of the bone marrow. It was recorded that "the only etiological factor was aspirin in 40-60 gr. daily dosage for over a period of years."

ASHWORTH and McKEMIE [1944]

A child, age 4 months, was given 0.17 g. of acetylsalicylic acid every 4 hours for four doses. Increased respiratory rate, loss of consciousness, acetoneuria, convulsions and cyanosis followed. Death occurred on the next day. Autopsy showed hemorrhages in the lungs, brain and heart; fatty degeneration of the liver; hyperplasia of the spleen; and hyperemia of the brain, adrenals, kidneys, intestines and lungs.

TROLL and MENTEN [1945]

A girl, age 2½, was given 150 gr. of acetylsalicylic acid in 6 days for bronchitis. Epistaxis, bloody stools, hematuria, convulsions, collapse, and coma followed. Autopsy showed massive hemorrhage in the region of the kidneys; petechial hemorrhages of the entire skin, brain, pericardium, and kidney and stomach mucosae; an enlarged thymus; acute splenitis; and toxic hepatitis.

THE TREATMENT OF POISONING BY SALICYLATE

In most instances of nonallergic poisoning by salicylate, no therapeutic measure is necessary other than discontinuance of the drug or, in rheumatic fever, a decrease in its dosage. For severe poisoning there is no specific remedial measure; treatment is largely symptomatic and consequently a great many drugs and therapeutic procedures have been used.

If the salicylate still remains in the stomach, it may be removed, as in any poisoning, by lavage (133, 135, 136, 208, 642, 731, 1320, 1447, 1662, 1687, 1754, 1757, 1823, 1997, 2027, 2096, 2240, 2304, 2533, 2742, 3214, 3342, 3344, 3651, 3681, 3835, 3915) but it is considered inadvisable in the early stages to add sodium bicarbonate to the fluid used for this purpose since it is possible, although not probable under these circumstances, that the alkali might increase absorption. For removal from the stomach, emetics have also been recommended (45, 170, 173, 194, 196, 225, 253, 278, 343). To much less purpose cathartics (86, 133, 135, 136, 642, 1320, 2011, 2027, 2199, 2966, 3197, 3344, 3610, 3681), enemas and colonic irrigation (91, 185, 977, 1019, 1754, 2011, 2742, 2966, 3214, 3235) have been suggested. For increasing elimination after absorption, diuretics—together with sodium bicarbonate which augments the renal excretion—have been recommended (86, 133, 3640).

To combat dehydration, large amounts of fluids, preferably containing dextrose and sodium r-lactate, may be given intravenously, by rectum or orally (99, 177, 208, 626, 642, 700, 903, 977, 1011, 1320, 1447, 1498, 1499, 1548, 1631, 1754, 1767, 1815, 1823, 2011, 2036, 2037, 2304, 2598, 2734, 3198, 3214, 3235, 3342, 3512, 3651, 3726, 3772, 3784).

Supportive treatment for cardiac failure may be necessary and the drugs recommended for this purpose in the literature reflect the current preference in such medicaments rather than their efficacy. They include camphor, caffeine, strychnine, digitalis and adrenalin (86, 99, 133, 135, 136, 876, 1320, 1548, 1631, 1687, 1823, 1957, 2304, 2531, 2734, 3214, 3342, 3344, 3835). Pilocarpine has been suggested as of possible usefulness (1754) and also stimulation of the skin (1876). Among the miscellaneous and nonspecific measures, sponging the skin to reduce temperature if there is hyperpyrexia is obvious and beneficial.

Other and Unidentified Salicylates

STURGES, cit. LANCET [1876 (3965)]

A man, age 27, was given about 16 g. of salicin for rheumatic fever. After the fifth day, delirium, coma, hyperpnea, cyanosis and convulsions occurred. Death occurred on the sixth day. Autopsy showed congestion of the brain, lungs and abdominal organs, and blood clots in the heart.

BEEBY, cit. LANCET [1877 (3966)]

A woman, age 25, with rheumatic fever of 4 days' duration, was given an average of 13 g. of salicin daily for 3 days. No drug was then given for 1 day and 30 gr. of salicylic acid with phosphate of soda was given every 2 hours the following day. The patient developed tinnitus, vertigo, epigastric pain, restlessness and delirium. Autopsy showed slight endocarditis, congestion of the lungs, and small patches of ecchymoses in the mucous membrane of the stomach.

SHAW [1887]

A woman, age 21, took salicin and sodium salicylate for acute rheumatism. After 3 days, delirium, auditory hallucinations, incontinence and hematuria developed. She died on the fourth night. Autopsy showed ecchymoses of the kidneys and bladder.

A woman, age 26, took about 1 g. of sodium salicylate for typhoid, changing the next day to salicin. The symptoms after the third day were delirium and hematuria. She died on the fifth day. Autopsy showed ulceration of the intestines and kidneys and hemorrhages of the kidneys and bladder.

KUNKEL [1899]

A woman, age 22, suffering from nephrosclerosis with cardiac hypertrophy, received 6 g. of salol for rheumatic fever. She developed drowsiness, albuminuria and dilated pupils, followed by dyspnea and coma. Death occurred on the third day. Autopsy showed fatty degeneration of the kidneys.

AUTENRIETH [1928]

A woman, age 22, took 8 g. of salol. Drowsiness and coma followed. Death occurred on the third day. Autopsy showed degeneration of the epithelium of the kidneys. The same case is described by Petri [1930].

LAWSON and KAISER [1937]

A girl, age 2½, with early rheumatic fever, was given small amounts of salicylates (not over 60 gr.) and oil of wintergreen was rubbed on her knees. After 7 days hyperpnea, vomiting, cyanosis, extreme restlessness and delirium developed. She had albuminuria, glycosuria and casts in the urine, and later anuria. The nonprotein nitrogen of the blood rose to 102 mg. per cent and the carbon dioxide content of the blood fell to 14 volumes per cent. Death occurred on the thirteenth day. Autopsy showed pleural effusion, pulmonary edema and atelectasis; congestion of the liver; and congestion of the glomerular tufts and degenerative changes in the convoluted tubules of the kidneys.

HARTMANN [1945]

Two infants were given salicylate therapeutically. Extreme hyperpnea, coma, convulsions, acidosis and ketosis occurred, followed by death.

THE TREATMENT OF POISONING BY SALICYLATE

In most instances of nonallergic poisoning by salicylate, no therapeutic measure is necessary other than discontinuance of the drug or, in rheumatic fever, a decrease in its dosage. For severe poisoning there is no specific remedial measure; treatment is largely symptomatic and consequently a great many drugs and therapeutic procedures have been used.

If the salicylate still remains in the stomach, it may be removed, as in any poisoning, by lavage (133, 135, 136, 208, 642, 731, 1320, 1447, 1662, 1687, 1754, 1757, 1823, 1997, 2027, 2096, 2240, 2304, 2533, 2742, 3214, 3342, 3344, 3651, 3681, 3835, 3915) but it is considered inadvisable in the early stages to add sodium bicarbonate to the fluid used for this purpose since it is possible, although not probable under these circumstances, that the alkali might increase absorption. For removal from the stomach, emetics have also been recommended (45, 170, 173, 194, 196, 225, 253, 278, 343). To much less purpose cathartics (86, 133, 135, 136, 642, 1320, 2011, 2027, 2199, 2966, 3197, 3344, 3610, 3681), enemas and colonic irrigation (91, 185, 977, 1019, 1754, 2011, 2742, 2966, 3214, 3235) have been suggested. For increasing elimination after absorption, diuretics—together with sodium bicarbonate which augments the renal excretion—have been recommended (86, 133, 3640).

To combat dehydration, large amounts of fluids, preferably containing dextrose and sodium r-lactate, may be given intravenously, by rectum or orally (99, 177, 208, 626, 642, 700, 903, 977, 1011, 1320, 1447, 1498, 1499, 1548, 1631, 1754, 1767, 1815, 1823, 2011, 2036, 2037, 2304, 2598, 2734, 3198, 3214, 3235, 3342, 3512, 3651, 3726, 3772, 3784).

Supportive treatment for cardiac failure may be necessary and the drugs recommended for this purpose in the literature reflect the current preference in such medicaments rather than their efficacy. They include camphor, caffeine, strychnine, digitalis and adrenalin (86, 99, 133, 135, 136, 876, 1320, 1548, 1631, 1687, 1823, 1957, 2304, 2531, 2734, 3214, 3342, 3344, 3835). Pilocarpine has been suggested as of possible usefulness (1754) and also stimulation of the skin (1876). Among the miscellaneous and nonspecific measures, sponging the skin to reduce temperature if there is hyperpyrexia is obvious and beneficial.

To control excitement and convulsions chloral hydrate, barbiturates, bromides, morphine and lumbar puncture have been suggested (99, 977, 1322, 1385, 1447, 1662, 1815, 1823, 2304, 2533, 2572, 2598, 3235, 3784). To the contrary, Guest, Rapoport, and Roscoe [1942], from studies on the action of barbiturates, paraldehyde and morphine on respiratory stimulation induced in dogs by salicylate, concluded that the administration of any hypnotic drug in the treatment of salicylate poisoning is inadvisable. They believe that salicylate increases the susceptibility of the central nervous system to the toxic effects of hypnotic drugs. Oxygen has been recommended as possibly beneficial for the hyperpnea in salicylate poisoning (99, 1631, 2100, 3214, 3342).

Alkalies, usually sodium bicarbonate, have been used most frequently in the treatment of salicylate poisoning (86, 133, 135, 136, 177, 208, 242, 243, 642, 876, 900, 903, 973, 1019, 1119, 1322, 1432, 1434, 1447, 1573, 1631, 1662, 1823, 1957, 1997, 2027, 2037, 2048, 2077, 2240, 2336, 2432, 2524, 2531, 2533, 2598, 2620, 2659, 2734, 2742, 2772, 2943, 2966, 3012, 3020, 3214, 3342, 3344, 3467, 3512, 3640, 3651, 3681, 3726, 3772). The alkali was intended primarily to counteract an acidosis which was believed to occur. The fact that sodium bicarbonate has often been effective therapeutically in salicylate poisoning tended to confirm the idea that the symptoms of poisoning were due to acidosis. It has previously been pointed out, however, that in all but the terminal stages it is probably not an acidosis but an alkalosis which occurs. The beneficial effect of sodium bicarbonate and of other alkalies is partially due to the fact that these substances increase the elimination of salicylates by the kidneys. A large dose of alkali may seriously increase the alkalosis while small and repeated doses may have a beneficial effect of reducing the concentration of salicylates in the blood without inducing severe alkalosis.

Inhalation of dilute carbon dioxide for combating the alkalosis, a logical measure, has not been suggested in the literature.

As ketone bodies have been found in the urine after poisoning by salicylates, the use of insulin or glucose or both has been advocated in analogy with the treatment of diabetic coma (133, 135, 642, 900, 977, 1011, 1119, 1341, 1432, 1434, 1447, 1573, 1662, 1767, 2240, 2277, 2531, 2598, 2620, 2659, 2734, 3214, 3235, 3342, 3344, 3726). Balázs [1930], Eichler and Bengelforth

[1938], and Graham and Morris [1933] stated, however, that no beneficial results can be expected from such treatment.

Shapiro, Redish and Campbell [1943 (3198)] have suggested the use of blood transfusion and vitamin K to counteract the hypoprothrombinemia of salicylate poisoning. Quick [1944 (2833)] has expressed the opinion that while vitamin K may be useful, it may not be the solution to the whole problem of hemorrhages in salicylate poisoning since such hemorrhages may occur in other ways than through hypoprothrombinemia.

Vitamin C has been used for the treatment of disturbances in the blood-clotting mechanism induced by salicylates, on the yet unestablished grounds of deficiency of the vitamin in poisoning by salicylate. Pelner [1942] reported on a boy with rheumatic heart disease who developed tinnitus and profuse nose bleeding on the third day of medication with sodium salicylate; on the administration of 300 mg. of ascorbic acid on each of two successive days the bleeding and tinnitus disappeared.

Shapiro [1944 (3195)] reported on a patient with acute rheumatic endocarditis who, on receiving 5 g. per day of acetylsalicylic acid, developed a hypoprothrombinemia; the prothrombin returned to normal when 400 mg. of ascorbic acid per day was given intravenously.

Under present knowledge the treatment of poisoning by salicylate is, as stated, largely symptomatic: gastric lavage if the patient is seen early; hydration; intravenous administration of sodium bicarbonate in small amounts to increase urinary elimination but with some caution in regard to the intensification of the alkalosis which may exist; intravenous administration of dextrose; supportive treatment for cardiac failure; sponging for hyperpyrexia; and the administration of vitamin K.

Allergic Poisoning: In the literature dealing with allergic poisoning by salicylates there is a paucity of suggestions for treatment. This is probably due to the fact that in many such reported instances the symptoms were not serious and disappeared without therapy in the course of a few hours. The most important step is immediate discontinuation of medication and complete avoidance of all drugs containing salicylates.

Emetics (1288, 3531), laxatives (1645, 1866), application of heat or cold (1288, 1339, 2218, 2536, 3531), cardiotonics and

stimulants (1162, 1339, 2148, 3531), enema (1288), oxygen inhalation (1162), hyposulfite and peptone (1229), fluids (1528), narcotics (708, 1288), and diuretics (1645) have been used or recommended in the treatment of allergic salicylate poisoning. Epinephrine, which is widely used in many idiosyncrasies, has been employed also to combat the symptoms of allergic poisoning by salicylates (484, 1162, 1288, 1320, 1447, 1776, 2003, 2536, 2805, 3216, 3563b, 3791). Prickman and Buchstein [1937 (484, 2805)], however, found that epinephrine is ineffective, and Goodman and Gilman [1941] express the opinion that epinephrine can be used successfully against urticaria and angioneurotic symptoms occurring in allergic salicylate poisoning but is ineffective for asthma.

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Nonfatal Poisoning, Sodium Salicylate:

10, 83, 102, 190, 195, 243, 675, 685, 727, 732, 803, 806, 929, 1075, 1119, 1229, 1253, 1276, 1322, 1381, 1434, 1499, 1736, 1817, 1821, 1876, 1967, 1987, 2011, 2036, 2127, 2194, 2201, 2244, 2299, 2308, 2339, 2402, 2432, 2447, 2489, 2494, 2513, 2531, 2559, 2659, 2699, 2706, 2716, 2734, 2772, 2883, 2928, 2943, 3029, 3059, 3063, 3130, 3203, 3341, 3423, 3589, 3652, 3707, 3772, 3855, 3856.

Nonfatal Poisoning, Acetylsalicylic Acid:

77, 177, 179, 342, 409, 424, 444, 632, 642, 731, 824, 902, 903, 916, 977, 1047, 1128, 1193, 1371, 1388, 1496, 1527, 1657, 1662, 1694, 1696, 1733, 1741, 1767, 1907, 1957, 2096, 2165, 2167, 2251, 2301, 2533, 2598, 2839, 2976, 2977, 2980, 3032, 3235, 3417, 3445, 3640, 3726.

Nonfatal Poisoning, Methyl Salicylate:

204, 903, 910, 1019, 1226, 1448, 1670, 1823, 1997, 2148, 2240, 2524, 2620, 2693, 2966, 3193, 3213, 3341, 3342.

Nonfatal Poisoning, Other and Unidentified Salicylates:

10, 107, 117, 177, 186, 190, 264, 408, 884, 964, 984, 1498, 1548, 1736, 1815, 1840, 1862, 2077, 2113, 2169, 2185, 2353, 2370, 2439, 2560, 2864, 2943, 3117, 3203, 3399, 3519, 3755, 3813, 3992.

Nonfatal Allergic Poisoning:

4, 37, 73, 211, 331, 363, 406, 453, 484, 492, 605, 694, 709, 731, 890, 929, 981, 982, 1028, 1033, 1086, 1159, 1165, 1179, 1183, 1190, 1288, 1339, 1455, 1520, 1528, 1560, 1618, 1645, 1736, 1768, 1776, 1799, 1826, 1866, 1878, 1891, 1958, 2003, 2077, 2106, 2127, 2147, 2181, 2218, 2250, 2309, 2415, 2420, 2465, 2506, 2536, 2643, 2646, 2805, 2808, 2846, 2925, 2952, 3012, 3204, 3208, 3216, 3267, 3275, 3344, 3482, 3531, 3556, 3563b, 3575, 3576, 3615, 3699, 3702, 3735, 3736, 3917, 3923, 3946.

The Question of Addiction or Habituation

THERE is considerable confusion concerning the definition of the words "addiction" and "habituation" as applied to the use of salicylates. Medical dictionaries often make no general differentiation between these words except, perhaps, that of degree. Sollman [1936] describes habituation as an increased tolerance due to repeated administration of the drug. Clark [1943] considers addiction a physical dependence, and habituation, a psychic dependence. Goodman and Gilman [1941] state that "in the addicted individual the presence in the body of the addicting drug is necessary to maintain normal cellular function." More precise definition of the terms "addiction" and "habituation" is necessary if they are to be, as they often are, extended and applied indiscriminately to drugs that are outside of the field of definite narcotics.

As used here, addiction is taken to mean a physical alteration caused by a property inherent in the drug itself, and as a consequence of which withdrawal of the drug results in symptoms of physiological origin. The term addiction should, it is believed, properly be reserved for such well-defined states as those occurring from the continuous use of morphine or other narcotic drugs.

In habituation, as used here, the reaction to withdrawal of a drug is psychological and does not arise from any inherent property of the drug itself. As pointed out by Goodman and Gilman [1941], "A large number of drugs are capable of producing habituation and if sufficient psychic influence is brought to bear, habituation may occur to pink water." Craving may occur occasionally in habituation, but not as a rule. Tolerance to a drug may occur without addiction or habituation, and addiction or habituation may occur without tolerance. Pathological changes may develop in habituation as a result of chronic poisoning, but the organism is not disturbed physiologically when the drug is withdrawn. An unstable person may have a tantrum if denied something to which he is habituated, and an individual with a continuous pain may suffer from anxiety or distress if his favorite analgesic is withdrawn. Such habits of use can always be interrupted without danger to health. The warning

against habit-forming drugs, however, in the minds of physicians as well as laymen, implies danger of addiction.

Clark [1943] was unable to find any proof in the literature that the chronic use of analgesic-antipyretic drugs produces physical dependence, although habituation or psychic dependence on the analgesic action has been indicated in a number of clinical reports. Wright and Montag [1942] considered acetylsalicylic acid the only coal-tar analgesic which is not habit forming.

Only a few instances appear in the literature in which "habituation" or "addiction" is attributed to the use of salicylate. Neumann [1909] described a patient who developed a craving for phenyl salicylate and cried for it when it was withdrawn. Pontius [1914] described "a nervous woman, aged 45, who for two years had been taking acetylsalicylic acid for neuralgic pains and headache, who had a mental condition similar to that of a morphine addict." Macht [1918] reported on a man who obtained relief from periostitic pains by taking acetylsalicylic acid. At first, 5 to 10 gr. was a sufficient dose, but later much more was required. This increase was attributed to habituation. Jackson and Pike [1922] described a patient who showed symptoms of salicylate poisoning after taking large doses of acetylsalicylic acid daily for a long time. The patient suffered from continuous pains due to a tubercular abscess on the neck. After withdrawal of the salicylate he craved the drug for some time. The case reported by Neumann appears simply as that of a hysterical woman, and the others as cases of dependence upon an analgesic drug for the relief of continuing pain.

Lowy [1934], from an inquiry which was answered by about one-fourth of all the hospitals in the United States, reported 0.45 cases of salicylate "addiction" per 100,000 admissions. "Addiction" was defined in the questionnaire as "popular use" or "popular habit." There can be no doubt that the label "addiction" was applied by many of those answering the inquiry to instances of frequent use or chronic poisoning.

The large quantity of salicylates and particularly of acetylsalicylic acid consumed each year in this country has occasionally led to the opinion that the drug is habit forming. Such a conclusion is without basis; statistics on the consumption of salicylate tell nothing about the consumers. In fact, the scarcity of reports of "addiction" or "habituation" to salicylates in a population consuming large quantities of salicylate strongly suggests that the drug does

not possess in any degree the property of addiction and is habit forming only to the extent that frequent use of any substance which gives relief, real or imaginary, from pain, is a habit.

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[See "Note on Reference Citations and on Use of the Bibliography," p. xv.]

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